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NUMBER 3

CLINIC OF DR. JAMES M. ANDERS

GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

SOME FORMS OF FUNCTIONAL CARDIAC DISTURBANCE: PREMATURE CONTRACTIONS; CARDIAC HYDROTHORAX. A. MYOCARDIAL. B. VALVULAR.

Importance of the Diagnosis of the Harmless Forms of Cardiac Disturbance; Cases of Unilateral Hydrothorax of Cardiac Origin.

THE diagnosis of the harmless forms of cardiac disturbance is of the highest importance. Unfortunately, it is these innocent affections of the heart which alarm patients far more than the serious, organic diseases of this organ. Hence, once the diagnosis of functional disturbance without associated myocardial or valvular lesions is made, the physician can and should reassure the patient; he should instil all of the optimism that he can command.

It should be distinctly understood by practitioners that an assured diagnosis is only possible with one skilled in cardiography. At all events, in every case the clinical diagnosis should be corroborated by the graphic method. The cases of simple extrasystole that one not infrequently meets with in the practice of internal medicine, of which I will show you an example this morning, afford an excellent opportunity for rendering real public service through psychic treatment—a branch of therapeutics which has been too much neglected. It is an unanswerable reproach on our neglect as a profession of proper attention to the psychic indications presented by our patients. (of which the decreasing confidence of doctors in medicine is a result.)

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public is quite aware) must be compensated by adopting the rational method of instilling optimism and teaching patients the value of hygienic measures, as well as the various forms of mechanotherapy and their limitations, so as to protect the public from pretenders and cults to which they are now rushing in incredible numbers.

The patient is a male aged sixty-seven years; a teacher; married; height 6 feet, weight 170 pounds. The family history reveals a strong rheumatic predisposition in the maternal ancestors. Mother had carried a mitral incompetency for several decades prior to death, which occurred at the age of sixty-seven, of erysipelas. Father died at seventy-six years of senile pneumonia.

The past history of patient shows that after the usual childish diseases he had chorea during the spring and summer seasons of three successive years—his tenth, eleventh, and twelfth years of age. In this connection it is worthy of note that chorea among children of school age is prone to develop in the spring of the year, especially in those of studious habits, as was true of our patient in his youth. At the age of sixteen years the patient had lobar pneumonia, acute articular rheumatism affecting only the knees at twenty-eight years, lasting ten days, without cardiac complications. Inclined to rheumatic pains, chiefly muscular, since then. In 1914 had acute lumbago lasting only two or three days, and influenza in 1918, from which he fully recovered in about two weeks.

Patient had been a moderate user of alcohol until the time of the enforcement of national prohibition, but has not taken any since; used tobacco to the extent of three or four cigars daily, but on one occasion, just twenty-five years ago, smoked half a dozen cigars between the hours of 8 P. M. and 1 A. M., followed by a tachycardia lasting twelve hours. Since then this patient, as is true of others in like circumstances, has been abnormally susceptible to the influence of tobacco. Not inclined to athletics, but during the last twenty years has taken moderate exercise in the open systematically; appetite normal, while digestion has been impaired since his youth.

His present illness began abruptly three months since, following upon an indigestible dinner, but not until he had retired about two hours later, when he experienced intermissions (*i. e.*, extrasystoles) in the heart-beats accompanied by a disagreeable nervous sensation referred to the precordial and epigastric regions. The premature contractions occurred at irregular intervals, but at times were cyclic, occurring every fourth, sixth, or tenth beat. At the end of about two hours they ceased to recur and patient slept well, as usual.

These symptoms returned each subsequent night after retiring for a period of one month, and then they began to be less severely felt and occurred at longer intervals, for example, every twelfth or more heart-beats, and for the last week they failed to reappear. It is of interest to note that only occasionally did extrasystoles occur in the daytime, and these exceptional extrasystolics were the first to disappear.

During the earlier portion of the course of his trouble gastrointestinal flatulence was rather well marked, and it was thought that the disturbances of the alimentary tract were the exciting cause of the extrasystoles. The blood-pressure was 136 systolic and 95 diastolic. Gentlemen, kindly feel of his pulse; you will find that the rhythm is perfectly regular, that the vessel walls are not distinctly palpable, and the pulse is of good volume. The urine analysis gave a negative result. Physical examination showed no abnormal signs, save only slight left ventricle hypertrophy and a moderate degree of pulmonary emphysema. An electrocardiogram made by Dr. Talley showed it to be normal in every particular, but the leads were taken during the day when the extrasystoles did not occur. The accompanying illustrations (Figs. 142-144) show leads I, II, and III. The patient, however, felt that the condition might be the forerunner of serious cardiac disorder. It is often difficult to allay the ill-founded fears of patients suffering nocturnal extrasystoles, but in the absence of previous definite heart lesions the outcome is almost invariably quite favorable under appropriate treatment. It is important to distinguish that variety of the disorder which is connected with hypertension and a weakened myocardium. In this form

the "dropped beat" may occur at any hour of the day or night, and its significance is far greater than in the case under discussion. In cases of premature contraction, which also manifest themselves during the day, physical exercise will, as a rule, cause them to disappear.

It would be, however, manifestly unwise to offer an absolutely favorable prognosis in this or similar cases of extrasystole



Fig. 142.



Fig. 143.

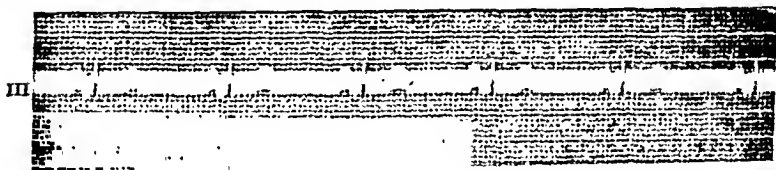


Fig. 144.

without taking the precaution to eliminate all serious cardiac lesions which may be associated. To do this successfully may require careful observation for a period of several months. On the other hand, in uncomplicated instances of "dropped beat" the patient can be, and it is important that he should be, as stated before, reassured that not the slightest cause for alarm exists.

The patient's diet was rearranged in such manner as to min-

imize the pure starches, and he was told to use a smaller evening meal than usual. The effect of the simply revised dietary was excellent, the gastro-intestinal flatulence slowly subsiding, with resulting disappearance of the extrasystoles. No medicines were prescribed, but the case afforded an excellent opportunity of rendering service by simply dieting the patient and from the psychic standpoint. In each individual case, functional or otherwise, the underlying cause, such as fatigue, tobacco, coffee, tea, dyspepsia, psychic influence, and the pathologic lesion in the heart and central nervous system, must be searched for until found, and to it the treatment must then be principally directed.

We shall next study 2 cases which illustrate a condition to which text-books and undergraduate teachers give scant attention, but one that is of considerable practical importance. I refer to unilateral hydrothorax without external dropsy or edema. I had long been impressed by the fact that hydrothorax in general is more common than is generally supposed, and also that it is commonly overlooked, when I, with the kind aid of Dr. Andrew Anders, made an examination of the postmortem records of 6132 cases in the Philadelphia General Hospital from all causes. The result was surprising; there were 608 cases of hydrothorax, or in 10.1 per cent. Of 267 cases of purely cardiac hydrothorax, to which group the cases we shall study this morning belong, the condition had been recognized in only 23 instances, or, at all events, had been noted on the history sheets in that number of cases. Of course, it may be claimed that these figures bear a definite and special relationship to the institution from which they were taken, but the obvious facts do not admit of a doubt that this condition is to an unjustifiable extent unrecognized. Again, the old notion that hydrothorax is usually bilateral must be abandoned, since my collective investigations showed that it is unilateral in 30 per cent. of the cases.

Case II., A. J., male aged sixty years; occupation hotel-keeper, for twenty-five years in a small town; married; height 5 feet, 10 inches; weight 170 pounds.

Family history furnishes no facts of clinical application.

Patient had all the usual childish diseases, with complete recoveries. Had two slight attacks of acute rheumatic arthritis, the first at seventeen and the second at twenty-eight years of age. Patient has no knowledge of any cardiac complications developing in connection with these illnesses, both of which ran a brief course. Had influenza in December, 1899.

Social history reveals two significant facts: (1) That he is a total abstainer despite the character of his business, and (2) that he has for many years been smoking to excess. Has never taken enough exercise out-of-doors to be worthy of mention, except that during the hunting season he would greatly exceed the point of fatigue by walking 10 to 20 miles daily. Appetite always good; also digestion until the onset of his present illness.

His principal complaint is of dry, irritative, non-productive cough and dyspnea, more especially at night, preventing sleep and inducing restlessness. These symptoms date from his last trip after game, when he became more fatigued than had been usual in the past. Slowly the above-named symptoms increased in severity after his return home. A physical examination when brought to the hospital a few days since showed, in brief, slight cardiac enlargement, but no apical murmur could be discerned. A subsection of the class has studied this case and has reported that signs of free fluid in the right pleural sac were noted, most probably a transudate; this has since been removed (amount $1\frac{1}{2}$ liters) and proved to be a clear amber-colored, serous liquid, with a specific gravity of 1012. In the absence of any elevation of temperature or local evidences of infectious inflammation the diagnosis of hydrothorax made by the subsection of your class is correct. The urine was found to be normal, although somewhat diminished in amount and the specific gravity 1025. Blood-pressure, 170 systolic, 105 diastolic; accessible vessels palpable. The blood count gave a normal result.

The clinical findings connected with the cardiovascular system point to chronic myocarditis, with the usual associated hypertension. In this instance, as so frequently happens, the dyspnea, restlessness at nights, and dry cough had been ascribed to the cardiac element alone, whereas these symptoms were greatly

relieved by a later aspiration. Such features as dry, irritative, unproductive cough and dyspnea, if found in association, should arouse a suspicion of hydrothorax and lead one to make a physical exploration.

The cases of cardiac origin are divisible into two groups: (a) myocardial and (b) valvular. Our patient presents no clinical indications of chronic valvulitis, but of myocarditis. It might be argued that the degree of dilatation in this case is not sufficient to explain the occurrence of hydrothorax. It has been, however, shown by Fetterolf and Landis that the serous fluid in this condition comes from the visceral and not from the parietal pleura or azygos veins; they also aver that greater frequency on the right side is due to the fact that dilatation of the right auricle is more common and more easy than a similar condition of the left side, and such dilatation is the only factor needed to cause damming back in the right pulmonary veins. In 13 out of a series of 16 cases of myocardial hydrothorax which fell under personal observation the transudate was wholly unilateral and right sided.

Before concluding, however, that myocardial changes are the sole cause in any given case, other etiologic factors must be excluded. I have long felt strongly that the various types of blood impoverishment are not infrequently accompanied by hydrothorax. Since many of these cases are unilateral and right sided, as I have observed, their immediate cause is most probably dilatation of right auricle. Our case, however, does not belong to this category, as shown by the blood examination. Neither is it an example of hydrothorax due to a pleuropulmonary tumor of whose presence there is not the slightest evidence.

By a process of exclusion, therefore, we arrive at the diagnosis of unilateral myocardial hydrothorax, unaccompanied by external dropsy or advanced cardiac decompensation. A systematic physical examination of the entire chest in all patients presenting themselves to internists and general practitioners, more particularly if troubled with dyspnea and a dry, non-productive, irritative cough, should be an absolute rule if we are to obviate the common blunder of overlooking hydrothorax. If doubt remains after

noting the physical signs, the chest should be needled—a simple operative procedure—which gives accurate information in hydrothorax, and aids, as in the case before you, to eliminate pleuritis with effusion in which there is an exudate containing fibrin and showing a higher specific gravity, 1015 or over. The use of the fluoroscope is also to be advised in dubious cases.

The prognosis is guardedly favorable as to life in this case, since it was met with during the early part of the stage of cardiac decompensation. If the balance of the circulation can be restored as the result of appropriate treatment, as is true of some cases, the patient may be comfortable and reach a symptomatic cure for an indefinite period of time. The causes of secondary dilatation, such as physical and mental overstrain, must be avoided. In decompensation accompanied with hydrothorax, of which our case is an example, however, death is inevitable soon or late in by far the majority of the cases, but it is not too much to claim that the early recognition of this complication and its prompt removal greatly assists our efforts to overcome the decompensation.

The treatment of the hydrothorax, which has caused the principal distressing symptoms, has reference to the indications presented by the underlying cause, the myocarditis plus the withdrawing of the serous transudate. It is the all too common custom of practitioners to rely upon the measures directed to the cardiac decompensation, such as rest, the use of digitalis, and saline laxatives. In my experience these are not only impotent to remove the serous transudate in most cases, but the digitalis and other stimulants tend to aggravate the dyspnea and restlessness if the serous collection is of any considerable amount. It was for this reason that we withdrew the fluid so soon as recognized and followed by the treatment of the cardiac element. We shall insist upon absolute rest in bed for one month at least. The patient will, at the end of that time, be enjoined to occupy the sitting posture for a fortnight before he resumes walking, which must be restricted to a short distance on the flat ground. In the event of the serous transudate reappearing, digitalis will be administered in medium-sized doses after a second tapping.

With the cardiac stimulants nitroglycerin will be combined, with a view to lessening the peripheral tension. In this connection the fact is [to be emphasized that cardiac decompensation with hypertension, as in this instance, does not present a contraindication to the use of digitalis and strophanthus. In all cases, however, trial should be made of absolute rest in bed alone, since this may restore compensation promptly. It is to be recollected that there is a strong tendency for the fluid to recur in hydrothorax, so that frequent tapplings are often necessitated, and should never be too long delayed.

Case III, like the previous one, is of cardiac origin, but due primarily to a chronic valvulitis and not chronic myocarditis. Statistics indicate that the incidence of these two cardiac forms is about equal. There is, however, a decided preponderance in favor of the myocardial variety if the unilateral cases without external edema are alone considered.

The patient is a man fifty years of age, married; occupation hotel proprietor; height 5 feet, 6 inches; weight 157 pounds (usual 175). Mother deceased at seventy-eight, cause of death unknown; father died of "stomach and bronchial complaints" at sixty-seven years of age; 4 sisters living and apparently healthy. Patient had the usual diseases of childhood; mild attack of typhoid seven years ago, and has not been well since then; he takes one cup of coffee and one of tea daily; smokes cigars with moderation; has used beer and whisky for many years to excess; pays some attention to diet and physical exercise.

The present illness began about three months ago, with coryza and dyspnea, frequently at nights, after exercise and when excited. Later he developed cough with slight mucoid expectoration; lost sense of taste and smell; speech became nasal in quality. Experiences discomfort after meals, with eructations of gas, which afford temporary relief; constipation alternating with diarrhea. The dyspnea has been more marked of late and is accompanied at times by cardiac palpitation. The lungs are emphysematous excepting the area occupied by the left lower lobe, as shown by the hyperresonant note, which I shall now elicit by percussion. Auscultation reveals prolonged expiration,

a feeble respiratory murmur, and a few wheezing râles over the hyperresonant field. These signs you may now note in order to familiarize yourselves the better with the case.

Gentlemen, I see that you have also discovered a flat note over the lower half of the left lung posteriorly. Observe now that the upper level of that field varies with a change of posture, it being distinctly lower when the patient assumes the dorsal decubitus, in the anterolateral line—a sure indication of the presence of free fluid. This is confirmed by the absence of vocal tactile fremitus over the same area. Again, on auscultation there is an absence of the respiratory murmur over the base. The presence of fluid has been further corroborated by a fluoroscopic examination by Dr. Pfahler.

I told you a few moments ago that unilateral hydrothorax was generally found on the right side of the chest. Here, however, is an exception, and one that is not infrequent. What is the immediate cause of this collection of fluid? Since hydrothorax is with rare exceptions caused by compression of the pulmonary veins due to cardiac dilatation, as previously explained, it will be necessary to examine the heart, which you will proceed to do for yourselves.

Having noted the physical signs referable to the heart, what diagnosis, if any, have you made?

Answer: Aortic incompetence.

The massive enlargement of the left ventricle which belongs to this affection is not so readily determined in this case, owing to the associated emphysema and left-sided transudate. Again, the diastolic murmur is less intense than usual on account of the emphysema. It is best heard with the patient in the upright bent forward posture, as is usually the case. While you are to be commended for recognizing the aortic incompetence in the circumstances, you have made no mention of the soft, almost inaudible mitral systolic murmur heard best at the apex-beat; this is most probably due to relative insufficiency at the mitral orifice occasioned by secondary dilation of the left ventricle. The presence of the latter murmur is indicative of decompensation. To account for the fluid in the pleural sac we have

marked dilatation of left ventricle and of the left auricular appendix compressing both upper and lower pulmonary veins.

Left-sided hydrothorax developing in the course of aortic incompetence without external edema is not infrequent, but too often overlooked. In this instance there can be no question as to the correctness of the diagnosis, and yet the possibility of the lung condition being a pleuritis should be thought of. Pleuritis, however, gives rise to a moderate febrile movement as a rule, and stitch-like pains in the affected side aggravated by deep breathing and coughing during the early stage, both of which symptoms were absent here. Physicians must grasp the pathologic fact that pleuritis is an infectious inflammation usually tuberculous in nature, while in hydrothorax the pleural membrane is uninflamed.

We shall now withdraw the fluid, using the Potain aspirator which is before you. This simple operative procedure can be safely done by any practitioner, but it should be carried out under strict aseptic precautions in all cases. A 2 per cent. solution of cocain is injected into the skin over the site it is proposed to enter. The sterilized forefinger of the disengaged hand is placed upon the rib below the interspace entered as a guide and the needle passed over it into the sac by a thrust in the manner I here show you. You will observe that a clear, amber-colored liquid is flowing into the bottle connected with the instrument. Having removed about a liter and a half of fluid, I shall take its specific gravity, which I find to be 1012. If this were a pleuritic exudate the specific gravity would be 1015 or higher. You will observe that the patient's breathing has been promptly relieved by the tapping of his chest. In view of the marked tendency to reappearance of the transudate we shall be prepared to tap the chest again, or as often as required. In the meanwhile absolute rest in bed will be insisted upon with a view to overcoming the cardiac exhaustion. This will be continued for one month at least. Subsequently, the patient's movements will be of the gentlest sort, under the strictest regulation. If rest fails to restore the balance of the circulation, digitalis in medium-sized doses (c. g., 10 minims of the tincture t. i. d.) will be employed. The

modern custom of administering massive doses of digitalis at long intervals is not to be thought of in the treatment of aortic incompetence.

In this case, as in all others, of hydrothorax a reappearance of the fluid is to be expected, but timely resort to tappings will afford the patient relief from such distressing symptoms as cough and dyspnea. Moreover, in this way the tendency to recurrence may rarely be overcome. In all cases life may be prolonged and rendered more comfortable. Lastly, I am prepared to state that when unilateral hydrothorax develops in the course of aortic incompetence it occurs more commonly on the left than the right side of the chest.

CLINIC OF DR. DAVID RIESMAN

PHILADELPHIA GENERAL HOSPITAL

ABDOMINAL MANIFESTATIONS OF THORACIC DISEASES

THE medical profession stands today, as it were, at the bar of public opinion, being judged as to the service it is rendering. Not able to see deeply, the public can but form its opinion from outward appearances; hence it is quite natural that it should be impressed by an occasional cure achieved by a charlatan or some member of an unskilled cult. And yet it must be admitted that to some extent the critical attitude of the public has at times some justification, for we do not always give what may be reasonably expected of us. The lay mind may be asking too much of us when it demands a cure for every ill, but it is justified in insisting on a correct or accurate diagnosis in most cases. Will the time ever come when, taking the better men of the profession, diagnosis will nearly always be right? It seems far off. But when we remember that in malaria, tuberculosis, syphilis, typhoid fever, and in the anemias the diagnosis is made almost infallible by physical examination, by the laboratory and the x-ray, may we not in the future hope for greater excellence, even if not for perfection, in diagnosing other diseases? However, in diseases of a less specific character than those mentioned above diagnosis will, I fear, ever remain subject to pitfalls, because, owing to the vast number of variables, the possible combination of symptoms is endless. For some diagnostic errors we may readily be shriven; for others, the laity will not forgive us; not because these errors are more avoidable, but because on the surface such errors are incomprehensible to all who are ignorant of the many difficulties that encompass our diagnostic efforts.

An illustration will make this clear and will at the same time bring me to the subject matter of my address.

Late one evening a call came to see a patient at a hospital under the following circumstances: A middle-aged man had been seized with violent pain in the right lower quadrant of the abdomen, with fever and vomiting. A diagnosis of appendicitis had been made, operation advised, and agreed to by the family, and the patient transferred to the hospital for operation. It being after hours, the operating staff was hurriedly called together, the operating room prepared, and, on account of the patient's prominence, a special anesthetist summoned from the outside. The anesthetist very properly requested a careful heart examination before he would proceed with the anesthesia. It was for the purpose of making this examination that I was called into the case. When I arrived the wheel stretcher was at the door of the patient's room and everyone was scrubbed up. Perhaps you are beginning to guess what I found upon examination. While the abdomen was distended and incidentally less tender on the right side than one might have expected, and while the heart sounds were weak, a surprise awaited me in the lungs. Anteriorly they showed nothing abnormal, but when I had the patient carefully turned over on his side I found a fair-sized patch of dulness in the lower lobe of the right lung over which bronchial breathing could be heard. The patient did not have appendicitis, but had lobar pneumonia. It was an embarrassing moment for all of us. The nurses and physicians were excused and the family was sent home after receiving a truthful but somewhat halting explanation which must have satisfied the doctor in the case, for he is still my friend.

Let us suppose the operation had been done, as others have been under analogous circumstances. Could the family have forgiven the error? To mistake a pneumonia for an appendicitis to the laity must seem a preposterous and unpardonable error, and yet to us, who are familiar with the difficulties, such a mistake is less heinous than others that the laity more readily condones. I thought by pointing out some of these dangerous diagnostic pitfalls that always lie in wait for us I might give a little help in time of trial, and a modicum of comfort in case of error, by showing how well nigh impossible the sick man sometimes makes it for us to diagnose his case correctly.

Pneumonia more often perhaps than any other chest trouble masquerades as an abdominal disease. In some of the cases I have met, as in the one related, belief that appendicitis existed was based on the occurrence of vomiting with pain and fever. Vomiting as a localizing sign has no value in children and but little in adults. I have observed that if the invasion of pneumonia occurs shortly after a meal it may be accompanied by vomiting, regardless of the age of the patient. There is but one royal road to correct diagnosis in such cases—a careful physical examination—and even that may fail in the first few hours because the characteristic pulmonary signs are not detectable; that is, dulness and the crepitant r le in the chest. If, however, one examines the patient with great care one may find a slight impairment on percussion and suppressed breath sounds on auscultation, signs that within twelve or twenty-four hours are transformed into the typical ones of lobar pneumonia. The abdomen, though often superficially hyperesthetic, is rarely tender on deep pressure, a point I have found of value in the case of children. A good full pulse, a flushed face, herpes, and headache suggest a supra- rather than an infradiaphragmatic condition. The trouble in the chest need not be lobar pneumonia; it may be pleurisy, empyema, or bronchopneumonia. A shadow of a doubt as to the existence of appendicitis or other acute abdominal condition, such as perforation of an ulcer, pancreatitis, etc., should be sufficient at once to attract attention to the chest and to cause a prompt revision of opinion. In the hospital one gets help from the portable x-ray apparatus, which will show a central pneumonia when physical examination gives only equivocal results. Leukocytosis is, of course, no help in the diagnosis between appendicitis and pneumonia, being common to both.

Pneumonia may simulate gall-bladder disease not only in the localization of the pain to the right upper quadrant of the abdomen but also in the presence of jaundice. In one such case a surgical colleague asked me as to the advisability of operating for the supposed gall-stone. but the patient showed a convincing patch of pneumonia in the right lower lobe. Sometimes there is

in lobar pneumonia rather sharp tenderness in the gall-bladder area which still further complicates the picture. It is not always easy to say what causes this tenderness. In some instances it is due to congestion of the liver with stretching of the capsule; in others, to a true cholecystitis.

Pleurisy, dry or wet, and empyema may cause just as much confusion as pneumonia; the pain in these cases is perhaps referred a little more often to the upper than to the lower abdomen. Diaphragmatic pleurisy, a somewhat rare condition, may closely simulate a hyperacute abdominal trouble, hemorrhagic pancreatitis, gall-stone colic, perforation of an ulcer. Careful examination may show in such cases that one side of the chest lags a little on inspiration; tenderness may be present on pressure over the phrenic nerve in the neck, and an *x*-ray examination shows fixation of the diaphragm on the affected side. However, the diagnosis may not become certain until it is made so by the appearance of fluid in the chest.

Among cardiac maladies there are several capable of causing symptoms that make the unwary sure the *fons et origo mali* is in the abdomen. Angina pectoris is one of these; it breeds trouble in two ways. The chest pain may be attended by epigastric pain and distention, simulating an acute gastric attack, or the pain may be located solely in the epigastric triangle, the so-called angina pectoris subdiaphragmatica. I shall not consider the justification of this questionable phrase, but desire only to point out that this pain may have the significance of real angina pectoris. The patient may locate the pain in the epigastrium, in the region of the gall-bladder, even in the loins, so that a hasty study of the case might lead to the conclusion that the patient was suffering from acute peritonitis, intestinal obstruction, gall-stone colic, or renal colic. Upon careful observation it will be noted that the pain radiates behind the lower sternum and that it is less colicky than vise-like, squeezing or burning; there is no tenderness on pressure in the upper abdomen and vomiting is not, as a rule, conspicuous. Yet in one case that I saw the patient vomited a good deal due to the fact that before the seizure—it was his first and last attack

of angina pectoris—he had eaten a very large and complicated meal. Profound anxiety or fear of impending death may be present both in angina pectoris and in acute abdominal conditions; yet if this subjective symptom is at all pronounced it throws the weight of evidence toward angina pectoris. The history of tobacco excess, of syphilis (a positive Wassermann), the presence of arteriosclerosis and high blood-pressure, the instinctive avoidance of all physical effort during the attack, perhaps a story that the patient has had more typical seizures of angina pectoris, all help in arriving at a correct conclusion. With regard to the last point, however, namely, a history of typical attacks, it must be remembered that angina pectoris usually maintains the character it starts with—in location of pain and radiation—from beginning to end.

Under the caption of angina pectoris a special place must be allotted to thrombosis or embolism of the coronary arteries, first, because it may produce symptoms almost exclusively abdominal, and second, because, though not an infrequent condition, it usually goes unrecognized. As a rule it presents itself as an intensely severe form of angina pectoris, with rapidly fatal termination. In such circumstances it may be considered a mere refinement of diagnosis. At times, however, it manifests itself chiefly by abdominal symptoms, and then, as a false interpretation may lead to operation, it is worth while to discuss the subject. The pain of coronary thrombosis, which is much more frequent than embolism, is sudden in onset, and if not in the precordial region is located in the epigastric triangle or a little to the right or left of it. Vomiting, shock and collapse, a slight leukocytosis, and fever may help to strengthen the diagnosis of perforation of an ulcer, acute peritonitis, acute pancreatitis, gall-stone colic, etc. Sometimes when the thrombus plugs the right coronary artery there is a little swelling of the liver. What will, in such a confusing combination of symptoms, put us on the right track? In a recent case the following symptoms proved of help in the diagnosis—an apprehension of death, a previously good digestion, obliteration of the dorsalis pedis pulse of one foot with a record of “sciatica” in the limb, a his-

tory of excessive smoking, and of great nerve strain. As another symptom suggesting a cardiac rather than subdiaphragmatic condition, this patient presented typical Cheyne-Stokes' breathing. Sometimes it is possible in a day or two to make out a pericardial friction sound. Finally, a careful examination of the abdomen does not reveal any cause adequately explaining the frightful suffering.

Rupture of the heart after infarction, also rupture of a saccular or dissecting aneurysm, may produce the picture of a subdiaphragmatic accident—rupture of an ulcer, gall-stone colic, acute pancreatitis, renal colic. There is intense unbearable pain in one or another of the abdominal regions, the occupying organ of which will be then held responsible for the trouble. The absence of local tenderness, radiation of the pain behind the lower sternum or into the shoulders may suggest the true nature of the case. A patient whom I had the opportunity of seeing with Dr. Gamble, of Haverford, Pennsylvania, and in whom autopsy revealed a rupture of a dissecting aneurysm, in his agony assumed the knee-chest posture, a symptom to which I shall in future attach a good deal of value.

Myocarditis with failing cardiac power usually manifests itself by shortness of breath on exertion, but in a fair proportion of cases the earliest and for a time the only sign may be a feeling of gaseous distention from which relief is obtained by belching. I cannot too strongly emphasize this point, for I have frequently seen cardiac patients urged on to physical exertion—to play golf, etc.—when the very opposite advice was needed. The patient himself sometimes contributes to the error in diagnosis by overemphasizing the digestive symptoms. I well remember a man, an engineer on the Pennsylvania Railroad, who was brought to me as a case of stomach trouble—he felt bloated and full after the smallest meal and was greatly troubled with gas. Examination showed that he had a well-marked cardiac enlargement and a considerable amount of fluid in the right pleural sac. Tapping of the chest and digitalis greatly improved his digestion.

A very remarkable abdominal mimicry is at times presented by mitral stenosis, as is illustrated in the following case: A patient

had been admitted to the hospital with a diagnosis of carcinoma of the stomach, and was to be operated upon by the late Dr. W. L. Rodman. Something in the case must have raised a doubt in Dr. Rodman's mind, for he requested a thorough physical examination of the patient. The task fell to me. I found tenderness in the epigastrium and a rounded mass, tender to touch, movable with respiration. This mass, taken with a history of vomiting and anorexia, could not help but suggest a gastric tumor. However, a careful examination showed the existence of mitral stenosis, and proved the epigastric swelling to be an enlargement of the left lobe of the liver. If that case were the only one of this type I should consider it a freak and a sport and not mention it here, but I have seen others; in one a diagnosis of carcinoma of the stomach, in another, of carcinoma of the liver, had been made.

I do not know why in some instances the brunt of the enlargement of the liver in cardiac decompensation falls upon the left rather than upon the right lobe. Whether the cause resides in the liver or whether adherent pericardium in some obscure way plays a rôle is as yet undetermined. Of course it goes without saying that in the cases I now speak of there is no edema of the legs, no ascites. Were these present, the confusion would not be so likely to happen. The liver often enlarges greatly and holds vast amounts of blood before any edema or serous effusion appears.

Some patients with auricular fibrillation complain of gastric distress, a sense of fulness, of bloating, and of tightness, which is apt to focus the attention both of the physician and the patient upon the stomach rather than upon the heart. It is well worth remembering that in the case of every middle-aged patient complaining of gastric symptoms, especially if there is a little shortness of breath on exertion, one should think of the heart.

Acute pericarditis sometimes simulates gall-bladder disease. I well remember a woman who had sharp pain in the region of the gall-bladder, in whom a day or two later a very definite to-and-fro pericardial friction was discovered. The course of the disease was that of an acute fibrinous pericarditis.

It may not be out of place to refer here to the abdominal masquerades put on by *tabes dorsalis*, although this is not a thoracic disease in the accepted sense. As a result of considerable experience it is my opinion that one should never diagnosticate intestinal obstruction, uremia, hysteric vomiting, gall-stone colic, etc., without first carefully examining the reflexes, and making, if necessary, a Wassermann test of the spinal fluid.

A surgeon friend of mine asked me to see an elderly lady who was suffering acutely from pain in the right upper quadrant of the abdomen, on account of which he had made a diagnosis of gall-bladder disease. As the patient had albuminuria and high blood-pressure, it was thought wise to try medical treatment. Upon examining her I found a few small red papules running from the median line in front outward toward the right. Although not vesicular, their arrangement suggested herpes zoster, a suspicion confirmed in a day or two by the appearance of a typical crop of vesicles over the lower right chest and upper abdomen. Other clinicians, for instance, Litchfield, of Pittsburgh, have described similar cases.

In rare instances caries of the dorsal spine may simulate an abdominal affection. A woman whom I saw complained of abdominal pain for which the appendix had been removed, but without benefit—the pain persisted. A careful examination revealed a small projection in the lower dorsal spine. Later symptoms of spasticity appeared. Under rest in bed and a proper brace the abdominal pain vanished completely, as well as the cord disturbances.

After this recital of anomalous cases, one might say, is there any disease that is typical? One of the first shocks that a recent graduate has is that text-book cases are few and far between. As he accumulates experience, if he so registers it on the tables of his memory that at the right moment the proper memory picture comes forth, then it does not greatly matter if disease often fails to be true to type; but for him who does not store his experience in an accessible place the path of practice is thorny indeed.

CLINIC OF DR. JOSEPH SAILER

DELIVERED IN THE COURSE OF CLINICS TO THE POST-GRADUATE
CLASS, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENN-
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SOME MISTAKES IN ABDOMINAL DIAGNOSIS

I HAVE grouped together some records of disease of the abdomen which serve to illustrate problems of diagnosis. In some of these the diagnosis was not made until after autopsy or operation. In others it was partly in error. In others the condition was unusual, and in some of these, because it was unusual, not suspected. No exact classification of these cases has been attempted, but they have been placed as far as possible in groups that have some common factor.

Physical examination of the abdomen has been somewhat neglected by writers and, I believe, to a certain extent by teachers and clinicians. This is largely because it is not easy to classify and arrange the physical signs as they have been classified and arranged in disease of the thorax. These physical signs are more vague, more variable, and, I think, as a rule more difficult to understand than are the thoracic physical signs, and yet greater difficulty should enhance the interest of abdominal examination.

It is an extraordinary fact that occasionally in abdominal disease no inspection of the abdomen is made. There are at least 2 cases in this list in which the absence of such examination led in both cases to the humiliation of the attending physician and in one of them almost to the death of the patient.

Large tumors of the abdominal wall are usually easy to diagnose. In pneumonia, hemorrhage into the recti muscles and sometimes into other muscles is occasionally found at autopsy. In all cases, in which I have requested that these hemorrhages be cultured, organisms were found, invariably pneumococci of

the same type as those which produced the inflammation of the lung.

One patient during convalescence developed a swelling in the epigastrium with all the characteristics of an abscess in the wall. The swelling was circumscribed. There was slight superficial subcutaneous edema, redness, tenderness, and fluctuation. The incision and culture confirmed the diagnosis of the pneumococcic abscess.

In another case a man of twenty-five had a tumor to the left of the median line just below the umbilicus. The skin moved freely over it. The tumor did not move passively or with respiration and was tender. The patient had fever and leukocytosis. A circumscribed intra-abdominal abscess was diagnosed adherent to the posterior wall, but an abscess between the rectus muscle and its posterior sheath was found. Cultures, unfortunately, were not made.

Small tumors of the abdominal wall are often difficult to recognize, particularly if there is much tenderness. A woman of forty-five years suddenly developed pain in the abdomen. There was frequent vomiting, constant nausea and extreme prostration, but no fever. The bowels were obstinately constipated and various purgatives were administered without result. A diagnosis of ptomain-poisoning was made. When seen, five days after the onset of the symptoms, the picture of intestinal obstruction was typical and a point of exquisite tenderness in the right lower quadrant suggested an incarcerated femoral hernia. There was a doubtful mass at this point. Immediate operation was urged, at which the incarcerated loop of intestine was still sufficiently viable to be returned to the abdominal cavity and the patient made a complete recovery.

Apparently too much emphasis has been laid upon the vomiting and no regard paid to the constipation.

A man thirty-eight years of age who had a specific history called upon me one morning complaining of pain in the right lower quadrant of the abdomen. There was exquisite tenderness and rigidity over McBurney's point. The leukocytes were 16,000. Temperature 102° F. A diagnosis of appendicitis was

made, and he was sent to the hospital for operation. Three consultants, including the surgeon who was to do the operation, concurred in the diagnosis. Upon incision in the abdominal wall a dark bluish-green mass was found whose exact nature was not immediately recognized. While it was being removed the scrotum was examined and only the left testicle found. It was decided then that the mass was an undescended testicle which must recently have undergone torsion or some similar condition that shut off the blood-supply and produced gangrene. The abdomen was, therefore, not opened, but the gangrenous testicle removed, and the patient made an uninterrupted recovery. We decided afterward that the mistake might have been made even although it had been known that the man was a cryptorchid.

Intra-abdominal abscess not connected with the appendix is sometimes puzzling. A young woman of twenty-six had had the Pel-Epstein type of fever for six months and had become emaciated to an extreme degree. No definite diagnosis had been made. Upon physical examination a small mass was felt in the left lower quadrant and vaginal examination proved that it moved with the uterus. A diagnosis of some form of abscess attached to the uterus was made. Reluctant consent was given to an operation, at which a dermoid cyst full of pus and hair was found. In view of the desperate condition of the patient no further exploration was made. She made a complete recovery, but for fifteen years has steadily refused to have the resultant sinus closed.

Another woman, a multipara, who had recently been delivered of a healthy child, was seen on account of intermittent fever, pyuria, and leukocytosis. A large tender mass was found in the left flank that extended above the costal margin, moved slightly with respiration and also passively. An abscess of the kidney was confidently diagnosed, but it was found that the kidney was fused with the spleen and that the two organs formed a communicating pus sac. It is possible that a more careful palpation of the tumor would have led to a suspicion of the true condition. Both organs were removed and the patient recovered.

Perforation of the intestinal tract is now commonly recog-

nized when it occurs, but sometimes it presents difficulties. A patient in the third week of typhoid fever had had sharp pain in the right lower quadrant. When seen several hours later there was no shock, no fever, no leukocytosis. The peristaltic sounds were loud and frequent. Especially because of the loud peristaltic sounds and the absence of any of the other usual signs of perforation, operation was delayed a precious twenty-four hours, at which time perforation was found in the ileum. Although the man was sturdily built, this organ was ptosed, lying, with a large part of the jejunum, in the pelvic cavity. The peritonitis that followed the perforation was limited to the pelvic cavity and had not spread, even at the end of twenty-four hours, to the abdominal cavity. The patient died two days later.

Circumscribed pelvic peritonitis rarely if ever inhibits peristalsis unless it is associated with obstruction. Therefore the presence of peristalsis should not exclude perforation. If the perforation is spontaneously cured by adhesions the symptoms may disappear with great rapidity. I possess the section of an ileum that I removed from a patient who had four perforations. Each was recognized, but the patient recovered so quickly that at the first three no operation was performed. At the fourth the signs were more severe and an operation was performed within a few hours, but it did not succeed in saving the patient. The first three perforations had been spontaneously cured by adhesions to the perforated area of the great omentum.

When the perforation takes place in such a manner that whatever contents escape are collected in a sac formed by adhesions the diagnosis may be very puzzling. A man of sixty years fell out of a tree. The resulting shock was ascribed to an already damaged circulation (he was a social drinker), and three fractures of the pelvis were diagnosed, but only by the roentgenologist. When seen two days after the accident the only definite findings were tympanites and metallic tinkling in the right upper quadrant. Peristalsis was normal, the bowels moved naturally, there had been some vomiting the first day, but afterward the appetite was fair. There was no fever and no leukocytosis, and except for the pelvic fractures, which did

not exist, a normal plate of the abdomen was reported. A diagnosis of acute dilatation of the stomach was made, for which, indeed, there was very little reason excepting the extensive area of tympanites and the metallic tinkling. Gastric lavage was advised, and after this the patient asserted that he felt relieved, although only 12 ounces of stomach contents were obtained. For five days he continued to improve, and was regarded then, one week after the accident, as probably out of danger. He then had a chill and when seen two days later had developed acute peritonitis and died in a few hours.

At the autopsy a perforation was found in the transverse colon and a large circumscribed collection of gas between the liver and the abdominal wall. This also contained some fecal material and very little pus. At one point the adhesions confining this gas tumor had yielded and the peritonitis had followed.

I have always felt that the diagnosis should have been made. The small amount of gastric contents obtained by lavage should have excluded gastric dilatation. The persistent tympanites in the right hypochondrium and the metallic tinkling should have indicated a gas abscess, that is, a subdiaphragmatic pyopneumothorax in an unusual situation in front of the liver. Operation should have been advised and probably would have prevented the subsequent peritonitis. Anxiety was lulled by the apparent improvement of the patient. In the presence of unexplained physical signs further studies should have been made.

A man with typhoid fever suddenly developed severe continuous pain in the epigastrium. A small tympanitic tumor was found that did not change its position or size in twenty-four hours. During this time the leukocytes increased, but there were none of the physical signs of perforation. When the abdomen was opened a strangulated Meckel's diverticulum was found whose tip was adherent to the abdominal wall. The patient died and an autopsy confirmed the other findings.

In this case also the correct diagnosis should have been made before the operation. With active peristalsis and free evacua-

tions there could have been no obstruction in the intestinal tract. A gas tumor, however, could only have arisen from the intestinal tract, and as there was no free gas in the peritoneal cavity, as the tumor was persistent and fixed in position, a distended adherent diverticulum should have been suspected.

Malignant disease of the abdominal organs occurs in so many forms that one is constantly on the alert. In obscure chronic cases, nevertheless, a diagnosis is made often only after considerable delay. There are certain features that seem to require emphasis:

1. Malignant disease may reach a considerable degree of development before the patient is actually incapacitated. In fact, it may sometimes be extensive while the patient still seems in good health.

2. Malignant disease may produce lassitude for a fairly long period without any other definite disturbance, so that in middle age such lassitude should always be regarded with suspicion.

3. Occasionally malignant disease is associated with a persistent fever for which no other cause can be discovered.

To illustrate the first statement, a robust man of middle age had been apparently in his usual health, but consulted his physician about some minor digestive disturbance. The latter found an enlarged liver. He had had no indigestion. His gastric contents were found to be normal and in all other respects he felt well and continued with his work. He had always been a total abstainer. I confirmed these findings. We both suspected malignant disease on account of the nodular character of the enlargement, but an exploratory operation was suggested and accepted. At this cancerous nodules were found in the liver, one of which was excised and sectioned. He developed later a hemorrhagic ascites rapidly recurring after paracentesis. No autopsy was permitted and the primary growth was never found.

A gentleman about seventy years of age, always active and energetic, had had an eye excised twenty-three years previously because of a tumorous growth in it, which was said not to be malignant. For a period of over six months he apparently lost interest in his usual pursuits. The change in his character was

quite noticeable, but he did not complain. One night he suddenly developed intense abdominal pain, and when seen the next morning the pain was obviously excruciating. Peristalsis was intensely active. There was no fever and the pulse only slightly increased. An enema of magnesium sulphate and glycerin was administered, and the evacuation of a large amount of scybalous feces relieved the pain immediately. Four days later he was again seen and an extreme degree of pallor was noted. An examination of the abdomen at this time revealed an enlarged nodular liver. For a period of five months this continued to enlarge, and during the last two months there were cerebral symptoms indicating metastasis to the brain. No autopsy was permitted, but it was assumed that a primary melanotic sarcoma had been present in the eye twenty-three years previously and that this malignant recurrence was of the same nature.

Of the third type there is the case of a young woman thirty years of age who had an inexplicable fever. This continued for six months and then enlargement of the liver was discovered. It was decided to perform an exploratory operation, at which numerous whitish nodules were found in the liver, one of which was excised and proved to be carcinomatous. Numerous blood-cultures were negative. She lived nine months after the operation. No evidence of a primary growth was ever found either at the operation or subsequently. All the tests were negative excepting the progressive moderate anemia. No autopsy was permitted. The temperature ranged between 97° and 103° F. and continued until the end.

It is, of course, well known by this time that carcinoma of the stomach may occur without the usual changes in the gastric contents, and it may even occur at an early age.

A man twenty-three years of age developed pyloric obstruction. The gastric contents showed an excessive amount of free hydrochloric acid. A cancerous mass was found at the pylorus and later metastasis to the peritoneum occurred. The histologic picture was typical not only in the section obtained at the time of the operation but also in that obtained later at the autopsy.

With the ascitic fluid obtained from this patient I injected a case of carcinoma of the stomach, with very marked but only temporary benefit. This was at the time that Hodenpyl obtained good results with the ascitic fluid obtained from an old woman.

A man of thirty-one years had severe epigastric pain one or two hours after taking food, associated with the regurgitation of food. The gastric contents contained an excess of hydrochloric acid and active ferments, and always some visible blood. The characteristic tenderness of ulcer was present. There was no palpable mass, but much anemia and emaciation and constant pain. A roentgengram showed marked deformity of the stomach and a diagnosis of ulcer was made. At operation a growth was found that resembled carcinoma occupying middle and upper portions of the stomach. In spite of a gastro-enterostomy the patient rapidly grew worse. There was evidence of metastases and shortly afterward he died. No autopsy was permitted, but the appearance was typically that of carcinoma, and both Dr. Jopson, the surgeon, and I felt reasonably sure of the diagnosis.

Impressions count for very little and statistics gathered from a very small number of cases are also practically useless, but at least I have the impression that carcinoma associated with the presence of free hydrochloric acid in the gastric contents occurs chiefly before forty years of age. In later life the presence of acid serves to make gastric carcinoma unlikely.

I may mention as an illustration the case of a man sixty-four years of age who had had gastric disturbance for some six years. Finally he had a very acute attack whose exact nature could not be determined. It was supposed at first to be gall-stones, but this diagnosis was subsequently dismissed. When I first saw him, about a week after this attack, he was comfortable, had no vomiting, but the x-ray showed a twelve-hour retention. A study of the gastric contents confirmed this and the fractional test showed a persistent and increasing secretion. The x-ray gave a permanent deformity of the duodenal cap. At the operation an ulcer of the duodenum adherent to the pancreas was found. There was no evidence of carcinoma.

Retroperitoneal tumors are usually painless and always fixed in position. They may occur in various parts of the abdomen. Sometimes they are smooth and sometimes nodular, and occasionally it seems as if there were two or more large masses. The rate of growth seems to vary. It must be recalled that the term "retroperitoneal sarcoma" is rather clinical than pathologic and that a number of morbid conditions are included in it. Even an autopsy, unless associated with careful histologic and even bacteriologic studies, may not be sufficient to determine the type of the growth.

A man of fifty years had a fixed nodular tumor in the median line just above the umbilicus. There was complete pyloric obstruction. The gastric contents contained no free hydrochloric acid, much lactic acid, and an abundance of Oppler-Boas bacilli. A diagnosis of carcinoma of the pylorus was made with confidence. It was supposed that the tumor had become adherent to the surrounding structures, although this is so rare in cases of carcinoma of the pylorus that suspicion should have been awakened. An operation with at least a palliative gastroenterostomy was suggested. The surgeon opened the abdomen and reported a tumor of the pancreas. Before he could go further the patient died on the table. At the autopsy the pathologist reported a normal stomach and pancreas, but he found a mass of enlarged peritoneal glands that had surrounded and compressed the pylorus. He diagnosed retroperitoneal sarcoma, but the bacteriologist stained some scraping from a gland and found tubercle bacilli.

In this case apparently a localized tuberculosis of the retroperitoneal lymph-glands had occluded the pylorus and given rise to all the symptoms of carcinoma.

Even less excusable was the error in a case of an aristocratic old lady who for years had used whisky daily as a tonic. A large smooth tumor appeared in the right upper quadrant, which did not move with respiration, was not tender, and there was neither ascites nor jaundice. This was regarded as hypertrophic cirrhosis of the liver. In a few months she died and a huge retroperitoneal sarcoma was found. The liver showed

moderate atrophic cirrhosis. The absence of respiratory motility should have corrected the diagnosis.

A woman of fifty-five years who had suffered for some time with chronic interstitial nephritis associated with high blood-pressure felt considerable pain in the right lower quadrant. When first seen for this condition a distinct mass was found in this region, which did not move with respiration, was only slightly tender, caused no intestinal obstruction, and was not associated with fever or leukocytosis. As soon as possible an operation was performed and an irremovable retroperitoneal sarcoma was found. This grew with great rapidity and in five months the patient died due to progressive weakness terminating in coma. No autopsy was permitted.

In this case as the tumor enlarged it appeared as a number of nodules, each smoothly rounded, and the general growth was upward and toward the median line.

A very similar condition was found in a woman of sixty-two years. In this case the diagnosis of inoperable carcinoma of the peritoneum was made and confirmed by exploration, but in neither was the diagnosis confirmed by the histologic study. The second case was complicated by a recurrent and severe ascites.

Tumors of the great omentum are often incorrectly diagnosed, probably because they are rare, they have no constant shape, their position is usually in the right upper quadrant or median line where other tumors are apt to occur, and the symptomatology is extremely variable.

An old man, febrile and emaciated, had a smooth mass with a sharp edge extending downward from the right lower margin, moving with respiration, not tender, and without ascites. No doubt was felt that it was an *enlarged liver*, but the autopsy showed a thickened, wedge-shaped, great omentum adherent to the lower edge of the liver.

An unmarried woman whose climacterium had been somewhat stormy and associated with much mental depression developed a tumor in the right side of the abdomen at about the level of the umbilicus. This tumor was somewhat irregularly rounded,

very slightly tender, moved passively and slightly with respiration. She had lost weight and strength. It required some time to obtain her consent to an exploratory operation. When this was done the great omentum was found massed in a large irregular ball firmly adherent to the right side of the transverse colon. It was supposed at the operation that it might be tubercular, but sections revealed that it was a carcinoma. It very rapidly recurred and the patient died some six months later.

A man of sixty-seven years was admitted to the hospital suffering from ascites. He admitted that he could and did drink more whisky than any two Irishmen. It was supposed that he had a cirrhosis of the liver, but the fact that there was a moderate febrile temperature and that on dipping some irregular masses could be found in the abdomen led the late Dr. Musser, who saw the case, to diagnose tubercular peritonitis. This was confirmed at autopsy and large masses tubercular in nature were found in the great omentum.

In cases of upper abdominal pain continuing for a considerable number of years, not associated with any grave progressive impairment in health, it will usually be found, if the pain is more or less continuous, that a duodenal or gastric ulcer is present, usually the former; and if the pain is paroxysmal, occurring as severe attacks, it is due to gall-stones. The ulcers are more common in men and the gall-stones more common in women. Frequently, however, it occurs that women suffering from paroxysmal attacks of pain over long periods of time will be treated for some other condition, usually some cardiac trouble.

An elderly lady of seventy-six years with a very bad heart had severe attacks of pain, sometimes in the chest and left arm and sometimes in the epigastrium. The attacks had been occurring for some years. The blood-pressure varied between 250 and 300 systolic. The chief condition was supposed to be angina pectoris, but the character of some of the attacks and the persistent tenderness in the right upper quadrant suggested an x-ray examination of the gall-bladder. A large shadow in the region of the gall-bladder indicated that a gall-stone was present. An operation was performed, the stone successfully removed,

and the patient lived for more than a year longer, finally succumbing to the heart lesion, but apparently grateful for the relief she obtained from her gall-stone attacks.

Another case, a woman of sixty-five years, had had paroxysmal attacks of pain in the epigastrium for over thirty years. They were apparently atypical. The x-ray revealed seven stones, four in the gall-bladder and three in a diverticulum. They were successfully removed from the two cavities and the patient made a recovery somewhat complicated by a persistent biliary fistula. She lived for several years after the operation, finally dying of an attack of pneumonia.

A woman of seventy-two years had a similar history of pain having lasted for forty years. The attacks had been very frequent and were always ascribed to the heart, and the patient was convinced that in one of these attacks she would die. In this case an enlarged gall-bladder could be felt. The systolic blood-pressure was high. There was a loud systolic murmur at the base of the heart. The gall-bladder was tender. There was no evidence of cardiac decompensation and after the removal of the gall-stones the patient was cured of her attacks. She is still alive six years after the operation.

Two other cases were both elderly ladies over sixty years, each of whom had suffered from pain in the upper abdomen for years, one severely and the other mildly. In one case the belief that the attacks were due to angina pectoris was dispelled with difficulty. Both have had their operations within the current year, and both, up to the present time, have remained in satisfactory health.

All of these patients have this in common, that they were elderly, that their attacks of pain had occurred for decades either in the retrosternal region or the epigastrium, in all, excepting one case, angina pectoris and cardiac decompensation had been diagnosed, and in only one was angina pectoris actually a complication.

It must not be supposed that paroxysmal attacks of pain in the abdomen always or even frequently mean gall-stones in the young. A young man of twenty-six years, remarkable for his

physical development and previously a celebrated football player, had attacks of abdominal pain. These attacks lasted only a few hours, but they were associated with a feeling of intense anxiety, apparently a fear of death. When first seen the attacks had occurred for about two years. He was having one during my visit. There was then marked tenderness in the left lower quadrant. Nothing was palpated. The peristalsis was normal. The temperature was normal. The leukocytes were at the upper limit of normal. Constipation was present. A diverticulitis was suspected, but the x-ray gave no confirmation. The attack subsided as promptly as usual.

A few weeks later there was another attack, and I then found the pain and tenderness in the median line just below the umbilicus. In all other respects the two attacks were similar. This was my last visit. Subsequently appendicitis and cholecystitis were diagnosed, but an exploratory operation revealed nothing abnormal. The attacks occurred more frequently and more severely, and finally death occurred. At the autopsy a strangulated hernia through a rent in the mesentery was found. The previous attacks were probably due to a loop of intestine temporarily caught in this rent. x-Rays were not taken during any attack, but it is doubtful whether they would have shown the condition if they had been. It was considered possible, after the patient died and the true condition was known, that he had been injured during a football game, but nothing definite was known.

Another case of torn mesentery was interesting partly because of the history and partly because of the results, although the working diagnosis was easily reached. This patient was an old lady in her sixties. An automobile in which she and six others were riding struck the end of a bridge and rolled down a steep embankment. Several of the occupants of the car were killed and none escaped without grave injury. She had altogether nine fractures, three of them in the pelvic girdle, and the shaft of the left thigh bone had united at right angles. She was first seen six months after the accident, and presented a most beautiful example of the hill and valley abdomen. Indeed, it resembled more the agitated surface of the ocean because the

hills were never stationary. She was constipated, but this was fairly well relieved by tincture of belladonna and olive oil. She suffered no particular pain. She was, of course, emaciated. A diagnosis of obstruction near the ileocecal valve, partial in character and of unknown nature, was made. Consent to an operation was later obtained. Dr. B. C. Hirst performed it, and found a large rent in the mesentery extending from the posterior wall of the pelvis to the ileum. Adhesions had occurred around the end of the rent. For a distance of about 3 cm. the mesentery had been stripped from the lumen of the ileum. The wall of the intestine had undergone a chronic hyperplastic inflammatory process and had become partly thickened, but its outside circumference was not increased. At the operation it was not possible to force the intestinal contents through the obstruction, nor could a probe, after the obstructed portion was removed, be passed through it. Nevertheless, she had had fairly copious movements of the bowels until the day of the operation. Above the obstruction the small intestine was distended and the wall showed a physiologic hypertrophy. Below it was much smaller, nevertheless an anastomosis was successfully accomplished. The edges of the rent were sewed together and the patient made a complete recovery from her intestinal condition, rapidly regaining weight and strength. No hernia had occurred, probably because of the numerous adhesions that had formed in the region of the tear. The histologic examination of the specimen showed only a chronic inflammation of the intestinal wall. It is needless to say that the true condition was not suspected.

Ordinarily obstructive lesions in the large intestines give rise to distention of the proximal portion and frequently metallic tinkling is heard in this region. This is apparently not always the case. In the presence of evidence of obstruction this should not lead to the exclusion of the diagnosis.

A man of fifty-seven years for six months had not felt well. A diagnosis of obstruction at the splenic flexure was made by x-ray. However, nothing apparently was done, and he subsequently entered the Presbyterian Hospital and placed himself under my care. It was found that he had a slight fever ranging

from 99° to 101° F. The leukocytes varied from 12,000 to 17,000 and they were chiefly polymorphonuclear. There was distinct tenderness over McBurney's point, but not elsewhere, and no mass or organ could be felt. His nutrition was good. The x-ray showed a sudden stoppage of the barium enema about the middle of the descending colon. There was no evidence of distention of the transverse or ascending colon, no metallic tinkling, and very little evidence of disturbance of the bowels. An operation was performed and a large carcinoma springing from the splenic flexure and involving the spleen, left kidney, and lumbar muscles was found. He died within twenty-four hours.

A very remarkable tumor in this area was diagnosed with more success, but the result was the same. A young man in the early twenties, on the service of Dr. Charles H. Frazier, was seen on account of a large palpable mass in the left upper quadrant. This mass was globular in size, moved slightly with respiration, the surface was smooth, the consistency firm, it was not tender. Upon percussion a dull tympanitic note was obtained in various regions, but in other places the note was flat. A diagnosis of endothelioma of the peritoneal coat of the intestines in this region was made. There was only slight intestinal obstruction. In these tumors, which are extremely rare, the intestine appears in the form of an irregular tunnel. Apparently the inability of the intestine to contract on account of the mass does not prevent the onward movement of the intestinal contents. At least this was the case in this instance, the only one of a tumor of this type that I have ever seen.

An operation confirmed the diagnosis. The tumor could not be removed, and further confirmation was obtained at the autopsy which followed shortly afterward.

Tumors in the right lower quadrant are perhaps less common, but not, however, always easy to diagnose. A clergyman thirty years of age was seen with a large mass in the right lower quadrant. This was globular, smooth, firm, flat on percussion, and fixed apparently to the iliac bone. It gave no shadow with the x-ray. One surgeon diagnosed sarcoma and refused to operate. Another surgeon performed an exploratory operation and found

an inoperable sarcoma attached to the ileum and, on account of its transparency to the *x*-ray, osteosarcoma was excluded.

The patient was then treated vigorously with radium, under which the tumor rapidly shrank and disappeared. In a year, however, it returned, did not yield to a second application of radium, and he soon died. At the end the patient had returned home and was no longer under my observation. No histologic study was made.

A woman of fifty-six years had felt some vague distress for about six months. There was nothing definite found on physical examination. Then a small tumor was detected in the right lower quadrant and an immediate exploratory operation was performed. This showed a retroperitoneal mass that was diagnosed sarcoma. It could not be removed. The tumor developed with great rapidity and the patient died in about eight weeks, profoundly cachetic and comatose for the last week. As the tumor was not incised and, indeed, merely inspected, it cannot be assumed that the operation materially hastened the patient's death.

Eventration of the diaphragm is not a very infrequent condition and it adds greatly to the difficulty of the diagnosis. The condition is primarily a hypoplasia of one of the lungs, which is usually otherwise anomalous, commonly having more than a normal number of lobes. As a result of this hypoplasia the diaphragm on that side rises and the heart is displaced toward the other side. If the eventration is on the left side it produces one of the types of dextrocardia. If on the right side, the displacement of the heart is less, but the liver dulness is higher. In all these cases the chest is symmetric and the respiratory expansion is equal upon the two sides. In the presence of abdominal pathology it may produce very extraordinary physical signs.

A young man with typhoid fever had dextrocardia and a tympanitic left thorax. The upper border of the area of tympany moved downward during inspiration. This is von Leyden's sign distinguishing between supra- and infradiaphragmatic lesions, that is, if the physical signs move downward during inspiration the lesion is below the diaphragm. Another physician who had examined the case had punctured twice for pneu-

mothorax. A diagnosis was made of left eventration, confirmed later when the patient died of typhoid fever.

The second patient was more extraordinary. An elderly woman, the wife of a clergyman, had ascites and right hydrothorax, both recurrent. If one was tapped, the other seemed temporarily diminished. The signs of ascites were characteristic. Those of hydrothorax were not characteristic, because faint breath sounds were heard to the level of the eleventh dorsal spine and there was faint transmission of the spoken voice. Serositis (Pick's disease) seemed unlikely, for there was no evidence of involvement of the pericardium. Perforation of the diaphragm was rather fanciful, although this condition was actually suspected. After some further study a guess was made of subdiaphragmatic hydrothorax, ascites, and right eventration of the diaphragm. Cirrhosis of the liver was suspected as the cause of the fluid beneath the diaphragm and in the abdomen. The x-ray confirmed this diagnosis and later it was established at autopsy.

A man of thirty-five years, head of a musical college, had had from time to time pain in the abdomen during which there would be distention. These attacks, his wife said, were always caused by mental distress. Otherwise he was unusually healthy and very active. On May 15th he was in a severe automobile accident. He had extensive lacerations of the right thigh, fracture of the anterior ramus of the pubic bone, and was profoundly shocked. One week after the injury he had an attack of collapse, with intense pain in the abdomen and some fever. Pneumonia was suspected, but the diagnosis was not established and he improved greatly in three days. Later he had a similar attack of the same vague character. During all this period his temperature never became normal. The pulse did not go below 100. The leukocytes ranged from 17,000 to 18,000. Gradually, however, he grew stronger, and on August 7th he returned to his home from the hospital and was able to walk with a crutch. On August 9th he had another attack of collapse similar to the two previous ones. There was intense pain in the epigastrium and beneath the right shoulder-blade. His pulse reached 140. There was no movement

of the bowels, no nausea, and no vomiting. He was profoundly shocked. He was first seen by me the following day. The upper half of the abdomen was rigid, particularly on the right side. The rigidity was board-like, and over this area there was considerable tenderness. The peristaltic sounds were very loud. If there was any difference in the expansion of the two sides, it was greater on the right. His heart was displaced to the left, the apex being in the fifth interspace in the midaxillary line, and the dulness extended from that point to the left border of the sternum. The pulmonic second sound was greatly accentuated, there was a diastolic shock, and a systolic murmur was heard at the pulmonic cartilage. Pulmonary resonance extended to the fourth rib in the right midaxillary line. From this point there was complete flatness as far as the sixth interspace and below this point tympanitic resonance. In the anterior axillary line the resonance extended to the costal margin and below this there was dulness. No breath sounds were heard over either the dull or the tympanitic area. Posteriorly dulness began at the ninth dorsal spine on the right and the eleventh on the left. There was no Grocco's sign. The right leg was much swollen, presumably due to the old injury. The leukocytes were 18,400, with 84 per cent. polymorphonuclears. He was immediately removed to the hospital. Another x-ray was taken, which showed the diaphragm at the fourth rib with a deep shadow beneath it. The lungs were clear. A diagnosis was made of some purulent condition in the right upper quadrant, whose nature was not known, and of right eventration. At the operation a distended gangrenous gall-bladder was found with a liver high in the thoracic cavity. The gall-bladder was drained, its inaccessibility precluding removal. The patient died and no autopsy was obtained.

Lesions of the urinary tract are not, as a rule, difficult, particularly in the hands of a competent urologist. A school-teacher fifty-six years of age had some discomfort in the right flank. A small mass could be felt and was diagnosed as the kidney.¹ The only remarkable feature in the case was the rapidity with which this mass increased in size, from being barely palpable

in the course of three weeks it reached a diameter of about 12 cm. A cystoscopic examination failed to show urine passing from the right ureter. A diagnosis of hydronephrosis was made and an enormously distended right kidney was found. It was not a uniform distention or cyst-like kidney, but appeared irregular, as if there were a number of cysts grown together, which was actually the case.

Another patient, a woman of thirty years, had been told that her case was hopeless and that she was suffering from some serious form of kidney trouble. She was well nourished, but extremely apprehensive. The physical examination indicated only a point of extreme tenderness in the left lower quadrant corresponding to McBurney's point. There was some flinching and slight rigidity, but no definite mass could be felt. The urine contained a trace of albumin, but was otherwise normal. There was no fever and no leukocytosis. In the hope of finding some focal lesion an operation was undertaken by Dr. B. C. Hirst. A fold of the sheath of the psoas muscle appeared to project upward as a sharp band and particularly to compress the left ureter. Above this point the ureter was only slightly distended and the pelvis of the kidney was not apparently abnormally large. This band was divided and stretched and nothing else was done. The patient made a complete recovery, with the disappearance of all tenderness, and fifteen years later is in excellent health.

It was not clear at the operation how the band of the muscle sheath could have produced the symptoms from which the patient complained, nor have we ever been able to discover any satisfactory explanation since then.

It is a well-recognized fact that thoracic lesions may produce symptoms of abdominal disease. Particularly is this the case in pleurisy, pneumonia, and endo- or pericarditis. It is not, I think, so well known that abdominal conditions may produce physical signs of thoracic disease.

A young woman twenty-two years of age developed ascites. She had fever, slight leukocytosis, and had become emaciated. A diagnosis of tuberculous peritonitis was made. There was found at the base of the left lung an area of dulness to percussion,

with bronchial breathing, bronchophony, and pectoriloquy. There were no râles. The fever did not exceed 101° F. A surgeon, because the signs pointed to pneumonia, was unwilling to operate, but I hazarded the opinion that the condition was one of pulmonary compression from the very extensive ascites, and that it would disappear as soon as the abdominal cavity was drained. At the operation we found the diagnosis to be correct. The pulmonary signs became normal immediately after the abdomen had been opened, and the patient, after a course of tuberculin, made apparently a complete recovery.

A somewhat similar condition was found in an elderly woman fifty-seven years of age. This patient had a large accumulation of fluid in the abdominal cavity apparently confined more to the left than to the right, which seemed to be located in the lower two-thirds. It had developed slowly. There was no fever and no pain. A diagnosis of probable ovarian cyst was made. Dr. VanBuskirk, of Pottstown, to whom the patient was referred for operation, was inclined to believe that it was a case of cirrhosis of the liver. We both discovered signs of consolidation at the left base, which I thought, in view of the absence of râles and particularly, in this instance, because there was no fever and no leukocytosis, were due to compression. Dr. VanBuskirk, therefore, operated and found a cirrhosis of the liver and a gall-bladder full of gall-stones. The signs at the base of the left chest disappeared as soon as the abdominal cavity had been emptied.

In this case the distention was not great, but nevertheless the compression had occurred.

Still more extraordinary was the case of a soldier at a base hospital in Vichy. This man was brought to the pneumonia ward delirious, with high fever and a high leukocyte count. There was flatness over the lower portion of the right lung, bronchial breathing, bronchophony, and pectoriloquy. A diagnosis of croupous pneumonia was made. The patient's symptoms were exceedingly severe, but there was no cough and no expectoration. It was suggested by a colleague that possibly the signs were due to an encapsulated empyema. An exploratory puncture was negative. The patient died. The right lung was

found to be entirely normal. In the upper portion of the right lobe of the liver there was a large mass, apparently some form of tumor, which had suppurated. The liver was greatly enlarged. A section was made of the rim of this growth, which indicated malignancy. Unfortunately, the specimen was lost and further study of the culture could not for some reason be made. The pulmonary symptoms, which had misled us all, were due to the enlargement of the right lobe of the liver and compression by it of the lower lobe of the right lung.

It may be useful to call attention to another condition that has given rise to puzzling symptoms. These are the abdominal signs associated with acute acidosis. Sometimes these simulate very closely the acute abdomen. The condition is by no means uncommon. Occasionally it occurs from some definite cause, particularly anesthesia, occasionally as a result of prolonged error in diet. Sometimes there seems to be no definite reason.

The first case was a prolonged postanesthesia intoxication. A girl of seven years had had her tonsils removed and apparently stood the operation well. There was no excessive hemorrhage. Two hours later she began to vomit. This vomiting was incessant and she became extremely weak, lying flat upon the bed, only turning the head from time to time in the effort to bring up a few drops of liquid, most of which seemed to be mucus. There was a mild elevation of the temperature. I saw her about twelve hours after the condition had started. At that time her physician had made a fatal prognosis, the surgeon was greatly distressed, and the family, of course, in a state of panic. The pulse was thready and frequent and the odor of acetone on the breath was very strong. The urine was obtained and the following morning was found to contain a large amount of diacetic acid and acetone, but before the report had been received the patient had been placed upon proctocylsis with 3 per cent. bicarbonate of soda solution. Improvement began in a few minutes and within an hour the vomiting had ceased and the patient proceeded to an uninterrupted recovery.

The result of this experience was a long paper on acidosis by the surgeon who had performed the operation.

The second case was far more alarming. I was called at 2 A. M. to go into the country to see a man who was supposed to be dying. The history was rather interesting. About six months previously he had consulted Dr. Combes, of Lausanne, Switzerland, who had placed him upon an almost pure carbohydrate diet for the purpose of relieving some obscure form of indigestion. The patient had been conscientious in following the treatment since that time. Some three days before I saw him he had had a chill followed by fever. Then there ensued rapidly epistaxis, hematemesis, hemoptysis, melena, and hematuria. The total amount of blood lost was probably considerable, because when seen the patient was blanched. The temperature was 103° F., he was vomiting and coughing blood, and the bed was bloody. The physical examination indicated the existence of a cavity at the left apex, but nothing else explaining the condition was found. The odor of acetone upon the breath was very strong. Although it was not regarded then as responsible for the hemorrhage and as possibly playing only a secondary part, the only thing that seemed feasible, in addition to the administration of morphin, was to give the patient bicarbonate of soda by the mouth and by the rectum. Hypodermoclysis was also given. The following morning horse-serum was administered, but by that time the hemorrhage had ceased and the temperature was rapidly declining to normal. By the end of twenty-four hours he seemed miraculously out of danger. He was then placed upon a more general diet and improved in every way, excepting that the signs of cavity persisted and there was cough with a mucopurulent expectoration. At first no tubercle bacilli could be found. Subsequently they became numerous, and the patient ultimately died of hemorrhage in the western United States at a comparatively high altitude, although he had been warned to avoid it.

This case is too complicated to ascribe it wholly to acidosis, but apparently the condition from which he suffered was in some way associated with the formation of diacetic acid, and when this was prevented recovery was apparently rapid.

The third and fourth cases apparently had no distinct causes.

A girl of fourteen years had a chill, followed by pain in the abdomen. There was almost constant vomiting, constipation, and rigidity of the abdominal wall. The physician thought of intestinal obstruction. The following day the rigidity in the abdomen was even more intense, the peristalsis was diminished, the leukocytes were 24,000, and there was albumin in the urine. At the second examination of the urine large amounts of acetone and diacetic acid were detected. On examination a systolic murmur was heard over the heart, there was no accentuation of the heart sounds, the lungs were normal, and there was diffuse rigidity in the upper abdomen, but no distinct tenderness. There was no definite evidence of any point at which the intestines could be obstructed.

The question of operation was very seriously considered, but it was resolved to give the patient large quantities of soda and wait twenty-four hours. Enteroclysis and soda by the mouth was administered and both were well retained. The temperature was normal and all the symptoms had disappeared twenty-four hours later.

I confess that in this case the rigidity, the high fever, and the leukocytosis all made me feel that the acidosis was merely a complication and not the cause of the condition. The early appearance of ketone bodies in the urine, the persistent vomiting without apparently any inflammatory or mechanical factor, and particularly the very rapid recovery all lead me now to regard the case as probably one of acidosis. A very careful examination by the physician in charge twenty-four hours after the institution of treatment failed to reveal any abdominal signs whatever.

A woman about seventy years of age, five years before the attack described, had a group of hydatid cysts removed from the liver, which had been mistakenly diagnosed cholecystitis. She made a complete recovery from this operation and remained fairly well. She was seized suddenly with intense pain in the right side of the abdomen. There was nausea, local tenderness, rigidity, and some fever. The leukocytes were not counted. The physical examination aside from the tenderness was entirely negative. The urine was examined and found to contain a con-

siderable amount of diacetic acid and acetone. The odor of acetone was not detected on the breath. Twenty-four hours after the administration of large doses of bicarbonate of soda by mouth the pain and tenderness had entirely disappeared. The temperature had become normal and the patient was able to eat her usual diet. There was nothing discovered that would explain the cause of this brief and moderately severe attack.

At the present time there is apparently no method of distinguishing between an acute acidosis associated, as it was in the third case, with high fever and leukocytes and a complicating lesion associated with acidosis. It must apparently be a matter of chance whether, in assuming acidosis as the cause, an acute inflammatory lesion is not overlooked. The improvement that appears usually within a few hours after the administration of the soda is perhaps the most suggestive differential point. In all these cases excepting the first I was extremely anxious until the patient was out of danger.

It should be remarked that in all 4 cases, seen in consultation at the patients' homes, it was impossible to make any tests for acidosis except the analysis of the urine for ketone bodies. The diagnosis, therefore, must be based upon the discovery of these bodies and the results of the administration of alkalies, not conclusive, but at least suggestive.

CLINIC OF DR. CHEVALIER JACKSON

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BRONCHOSCOPIC CLINIC

Asthmatoid Wheeze Diagnostic of Foreign Body in the Bronchus (Case No. Fbdy. 861).—This woman, aged forty-four years, while eating pork pie four days ago felt something hard lodge in her throat, producing a choking and coughing attack that lasted about an hour and a half. Since that time she has had no symptoms except a slight cough, during which she has noticed an unpleasant odor of cooked pork. There has been no pain, no temperature elevation, no difficulty in swallowing. Upon placing the ear at the open mouth of the patient a wheezing sound is noticed increasing at the end of a prolonged forced expiration. This is known as the "asthmatoïd wheeze." It is not dependent on secretion and is often louder and more distinct after the secretions are removed by expectoration. The chest has been examined by Dr. Stengel, who reports diminished expansion, impairment of percussion, diminished intensity of breath sounds with a prolonged expiratory, wheezing râle—all of these signs on the right side; while the physical signs on the left side are normal. These signs indicate obstruction of the right stem bronchus.

Dr. Pancoast finds a faint shadow which he believes to be a not very dense foreign body in the right bronchus (Fig. 145).

Diagnosis.—Notwithstanding the patient is almost symptomless, the diagnosis is positive for foreign body. It is difficult to realize that a sharp, rough, putrid bone can be obstructing a bronchus and abrading the bronchial epithelium and yet the patient have so little cough, no expectoration, and no rise of temperature. This almost symptomless interval between the

initial paroxysm of choking and coughing and the later gradual onset of symptoms of drowned lung and pulmonary



Fig. 145.—Roentgenogram showing a piece of pork bone in the right bronchus of a woman aged forty-four years (Case No. Fbdy. 861). The bone produced the asthmatoïd wheeze which is diagnostic of a foreign body in the bronchus. Bone removed by peroral bronchoscopy under local anesthesia in thirty-five seconds. (Plate made by Dr. H. K. Pancoast.)

abscess is the rule, not the exception. A diagnosis of foreign body in the lung in this case is based upon the following points:

1. The asthmatoïd wheeze heard by the examiner at the open mouth of the patient.
2. Physical signs of obstruction of the right main bronchus elicited by Dr. Stengel.
3. A suspicious Roentgen-ray shadow corresponding to the right stem bronchus.
4. History of choking on a hard object while eating.
5. Subsequent slight cough with subjective odor of pork becoming putrid.
6. All of the foregoing phenomena date from the choking, in a person previously in perfect health.

The first three points enumerated would be sufficient to establish a tentative diagnosis of foreign body, even if there were no history of foreign body in the case.

Prognosis.—If the foreign body remains in the lung it will eventually prove fatal, not from pneumonia, but from pulmonary abscess. If removed by bronchoscopy recovery is certain.

Treatment.—Bronchoscopic removal is clearly indicated. No other treatment is worthy of a moment's consideration. Waiting for the foreign body to be coughed up is hopeless, because it occurs in less than 2 per cent. of the cases. The mortality of mediastinal bronchotomy in such patients as this one is close to 100 per cent. The mortality of bronchoscopy carefully done, in such a patient, is nil.

Bronchoscopy.—A little cocain has been applied to the pharynx. I now insert the laryngoscope and apply cocain to the larynx, trachea, and right bronchus with a long applicator. I then pass the bronchoscope and find the bone in the right bronchus. Noting the forceps spaces are located laterally, I insert the forceps so that the jaws will open laterally; with them I seize and remove the bone. My instrument nurse, Miss Holman, tells us the bronchoscopy required thirty-five seconds. Now you see why I said no treatment other than bronchoscopic removal was worthy of a moment's consideration. Diagnostically it is interesting to note that the asthmatoïd wheeze is gone. The bronchoscopic appearances of the bone *in situ* in the bronchus is illustrated in the color plate.

DESCRIPTION OF PLATE 1

Bronchoscopic Clinic at the University of Pennsylvania Hospital

By CHEVALIER JACKSON, M. D.

Photoprocess reproduction of the author's oil-color drawings:

A. Influenzal tracheobronchitis simulating diphtheria in a child aged two years. Antitoxin had been given because of the erroneous diagnosis. The direct laryngoscope reveals the swollen subglottic tissue that produces the croupy cough and the stenosis in laryngeal diphtheria; but there is no membrane or erosions on the intensely inflamed, slightly cyanotic mucosa.

B. Cancer of the esophagus as seen through the esophagoscope in a man aged fifty-five years, referred to the Bronchoscopic Clinic by Dr. Stengel. The fungations were nipped off, and, on histologic examination, confirmed Dr. Stengel's clinical diagnosis of cancer.

C. A typical endoscopic picture of chronic bronchitis after removal of collected secretions. The patient is recumbent. The upper orifice is that of the middle-lobe bronchus. The lower two-thirds of the drawing represents the view into the lower-lobe bronchus with subdivisions deep in the lower lobe. The branch-bronchi give off dorsal and ventral branches below the orifices shown. The thickening of the dividing spurs usually accompanies chronic bronchitis.

D. Papillomata on the left side of the fauces of a child aged two years. These faucial growths appeared after the removal of the recurrent multiple laryngeal papillomata from the larynx shown in illustration E. The appearance of new growths at so remote a location indicates the sad mistake of ruining a child's larynx in the attempt to prevent laryngeal recurrence by radical removal of the normal tissue underlying the base of the growths in the larynx.

E. Direct laryngoscopic view of a mass of laryngeal papillomata overhanging the glottis of a child aged two years. The dropping of the mass into the larynx on inspiration caused the cyanosis of the mucosa. The croupy cough and the dyspnea led to an erroneous diagnosis of diphtheria, for which antitoxin had been given. Removal of papillomata from the larynx is followed for a time by local repullulations and new growths at new locations (see illustration D); but repeated superficial removals will result in a cure with perfect voice. Radical local removal will not hasten the cure and will ruin the voice.

F. An aspirated piece of bone wedged in the right bronchus of a woman aged forty-four years. The bone produced the diagnostic asthmatoïd wheeze. Bronchoscopic removal of the bone required thirty-five seconds and was immediately followed by disappearance of the asthmatoïd wheeze.

G. Bronchoscopic view of a fistula leading to an old pulmonary abscess, not of foreign body origin, in a man aged fifty years. Bubbles of pus were coughed out of the orifice of the fistula just before the image here shown was mentally recorded by the bronchoscopist. The granulations here seen lined the fistula leading to the abscess, the "cavity" of which was filled completely, not simply lined, with mushy granulation tissue.

H. Bronchoscopic view at the bifurcation of the trachea in a case of pulmonary tuberculosis. Pus is blown out of the right upper-lobe bronchus by cough. The thickened, broad carina, the pale, anemic, cyanotic mucosa, and the visibility and dark color of the mucosal vessels are all characteristic of advanced pulmonary tuberculosis.

I. Esophagoscopic view of a blackened, corroded, open safety-pin in the esophagus of a child aged seventeen months. Had removal or pushing down been attempted by any blind method, such as with the Graefe basket, bristle probang, sound, or stomach-tube, the point of the pin would have produced a fatal perforation of the esophageal wall. With the esophagoscope approach under guidance of the eye insures safety, provided the utmost care is taken not to touch or override the pin with the tube mouth. Removed esophagoscopically without anesthesia, general or local, in one minute and fifteen seconds.

PLATE I



A



B



C



D



E



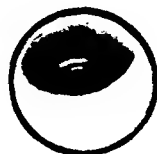
F



G



H



I

For description, see facing page

both lungs. As you know, ether anesthesia is very safe so long as the airway is maintained clear of obstruction. One of the chief duties of an anesthetist in giving ether for general surgical work is to maintain a clear airway. Many deaths have occurred from attempts to etherize a dyspneic patient who is depending more or less on his voluntary muscles for aid in his fight for air. Respiratory arrest in such cases is usually fatal unless an expert tracheal surgeon is at hand to clear the airway. For the bronchoscopic removal of the peanut kernel from the trachea of this child cocain is out of the question because of the toxic dangers of cocain in children. The newer local anesthetics are unsatisfactory when simply applied to the surface. Moreover, the application of any local anesthetic takes more time and causes a child more distress than to introduce the bronchoscope and take the foreign body out. Furthermore, as you will see in a later case today, bronchoscopy is not a painful procedure. Therefore, we will proceed without anesthesia, general or local.

I introduce the bronchoscope into the trachea. The free admission of air through the bronchoscope, which represses the swollen glottic walls, carries the peanut kernel to the bifurcation of the trachea, where it obstructs both main bronchial orifices. Quickly introducing closed forceps I tilt the peanut kernel so that it presents endwise, this allows air to enter both lungs and at the same time opens up a pair of forceps spaces, one to the right of the kernel and one to the left. Inserting the forceps jaws into these respective spaces, I grasp the peanut kernel with a forceps pressure that I feel is sufficient to hold it securely against being stripped off at the glottis and yet not sufficient to crush it, bringing the peanut kernel against the distal tube mouth. The nut kernel, bronchoscope, and forceps are all three withdrawn as one piece. Miss Holman tells us the time required from the moment of the introduction of the bronchoscope is two minutes and five seconds.

Open Safety-pin in the Esophagus (Case No. Fbdy. 889).—This seventeen months old baby, while being bathed by the mother, choked and gagged. There were open safety-pins on the table within reach of the child. The mother felt a safety-

pin in the child's mouth, but her efforts to remove the pin pushed it farther down. Since the accident the child has been able to swallow liquids, but solids are regurgitated. There has been no fever and no other symptoms. Often in these cases the swallow-



Fig. 146.—Roentgenogram showing open safety-pin in the esophagus of a baby aged seventeen months (Case No. Fbdy. 889). The lodgment point downward is a potentially dangerous one because of the tendency for the slightest pressure to drive the point into the esophageal wall. Removed by esophagoscopy without anesthesia in one minute, fifteen seconds. (Plate made by Dr. H. K. Pancoast.)

ing is normal and the symptomless condition of the patient often leads parents and physicians into the error of thinking no foreign body is present. All such cases should be subjected to a thorough Roentgen-ray examination from the nasopharynx to the tuberosities of the ischia.

Dr. Pancoast's roentgenogram which I show you here (Fig. 146) shows the open safety-pin lodged in the esophagus below the cricopharyngeal constriction. You will notice that the point is directed downward. This makes closure easy by withdrawal into the tube; but it makes of the case a most dangerous one for esophagoscopy if the utmost precautions are not taken to avoid overriding the foreign body or hitting it with the tube mouth. Any of the obsolete blind methods with bristle probang, Gracfe basket, or sound would inevitably be fatal. The ability to see through the esophagoscope renders esophagoscopy safe in careful hands.

Esophagoscopy.—I pass the esophagoscope with the utmost caution, inspecting every fold on the way down until the pin is reached. I make sure that the presenting part is the spring end of the pin; then noting the forceps spaces are anteriorly and posteriorly placed I insert the forceps accordingly and withdraw the pin. As no anesthetic was used and as there has been no trauma inflicted by the pin in its sojourn in the esophagus nor in its esophagoscopic removal, the child will start on the return journey to its home in the West tomorrow. Miss Holman tells us the esophagoscopic removal of the pin required one minute and fifteen seconds. The esophagoscopic appearances of the safety-pin are illustrated in Plate 1.

Laryngeal Stenosis Due to Faulty Tracheotomy.—This child, aged two years, about a year ago had a laryngeal diphtheria, with such severe dyspnea that tracheotomy was required. We did not see him then; he has been sent to the Bronchoscopic Clinic because the tracheotomic cannula cannot be abandoned. When an attempt at decannulation is made he starts to asphyxiate because he cannot get air through his stenosed larynx. This stenosis is partly cicatricial and partly cartilaginous. We will send the child out while we discuss his case.

On looking at the position of the cannula and the tracheotomic scar we find that the tracheotomy was done through the larynx instead of through the trachea. This kind of faulty tracheotomy is the cause of most of the cases of chronic laryngeal stenosis. The acute stenosis would have in all probability sub-

sided and the cannula could have been abandoned inside of two weeks had a low tracheotomy been done.

In diphtheria the stenosis, as I discovered many years ago with the direct laryngoscope, is due not to accumulated membrane, but to swelling of the subglottic tissues. When a high tracheotomy is done and a cannula is worn in this inflamed area, sloughing, perichondritis, and chondrial necrosis follow the secondary mixed infections.

The tracheotomy saved the child's life and it ill becomes anyone to criticize the work of the man who saved it; but it is the duty of a teacher to teach how work can be improved upon. It is my duty to tell you that tracheotomy, one of the oldest operations in surgery, is today more often done badly than any other operation. *High tracheotomy* should never be taught. The distinction between high and low tracheotomy is a relic of the days when it was considered a formidable operation to divide the isthmus of the thyroid gland. There is only one tracheotomy and that is always low, always below the first ring. The cricoid should never be cut because it is the only complete ring in the whole airway. Cutting it is a frequent cause of stenosis. Emergency tracheotomy should not be a stabbing. A two-stage finger-guided operation is better and just as quickly done. The whole front of the neck should be split open exactly in the middle line and the trachea felt for. It is quickly found in a large wound if Jackson's tracheotomic triangle is memorized.

We will now bring in the child and proceed to treat the stenosis of his larynx with these bougies passed through the laryngoscope. It is necessary bronchoscopically to inspect the trachea occasionally and to remove granulation tissue if any is present. You will notice the child murmurs somewhat, but he does not cry or clench his teeth. He knows what is coming, having experienced it before; but he opens his mouth and lets me insert the bronchoscope and inspect his trachea. I now ask him if I hurt him, and you hear him say "No." By this criterion I know that bronchoscopy without anesthesia, general or local, is not a painful ordeal. I shall now pass the laryngeal bougies. This kind of bouginage will cure about 90 per cent. of the cases

of laryngeal stenosis in which there has not been too much destruction of cartilage, but many such treatments will be necessary for cure. Some of you may wonder at the clearness and loudness with which the child said "No." The cords were unimpaired by the original condition; and it is one of the great advantages of this treatment by direct laryngoscopic bouginage that the voice is retained or restored, not impaired.

Hiatal Esophagismus (So-called Cardiospasm); Ulcerative Esophagitis; Chronic Gastritis with Erosions.—This soldier, aged twenty-seven years, was suddenly seized with difficulty in swallowing. Food would be regurgitated within a few hours after swallowing, sometimes bringing with it food that had been swallowed days before. This was not vomiting, because the food had never reached the stomach. It is necessary to distinguish between regurgitation and vomiting. When the patient first came I passed the esophagoscope and found the following lesions:

1. A dilated esophagus.
2. Esophagitis, with furred, pasty-looking epithelium, and superficial erosions.
3. Spasmodic stenosis of the esophagus; chronic gastritis with erosions on the lesser curvature.

There was no narrowing and no spasm at the cardia, therefore the name "cardiospasm" is not applicable to this case, and I doubt if it is every properly applicable to any case. There was, and is occasionally yet, a spasmodic stenosis at the hiatus esophageus; but there were in this case undoubted lesions to cause the spasm by reflex activity; therefore, it is not a pure neurosis. Undoubtedly there are a number of different conditions heretofore grouped under the misnomer "cardiospasm." Mosher has shown that organic abdominal disease, especially of the liver, can, and does in many cases, produce an organic stenosis with all the symptoms that have been grouped under the name cardiospasm. In this particular case there seems to be a true spasm, but it is located at the hiatus. The patient is almost free from trouble now after some months of treatment by the esophagoscopic dilatation of the hiatal constriction with the

application of argyrol and later chlorolyptus to the erosions and inflammatory areas. The manner of doing this you will now see.

Esophagoscopy.—The esophagoscope passes readily down the esophagus; the mechanical aspirator acting through the canal in the wall of the esophagoscope withdraws the fluid encountered in the esophagus. The esophagoscope hesitates at the diaphragm, but the spasmodic closure yields to gentle continuous pressure and the esophagoscope glides almost unaided into the stomach without encountering any resistance whatever at the cardia. Passing a swab saturated with 2 per cent. solution of chlorolyptus, I apply it to the erosions in the stomach and, during withdrawal, to the esophageal lesions. The outside of the tube passed measures 10 by 14 millimeters, which affords considerable mechanical dilatation. Some cases require the use of a dilator passed through the esophagoscope.

Carcinoma of the Esophagus Mistaken for Gastritis.—This man, aged fifty-five years, was treated before admission for stomach trouble because of supposed vomiting, which was really regurgitation; the food came back up before it had reached the stomach. On passing the esophagoscope I discover in the esophagus at the level of the left bronchus a fungating, bleeding, ulcerated lesion that I believe to be cancer. To verify the diagnosis I take a specimen for biopsy with this cutting forceps. This procedure involves no risk because I remove only the fungating part.¹ If the histologic report comes back positive for malignancy, as I have no doubt it will, this patient will be treated by radium, cancer of the mediastinal esophagus being inoperable. Miss Holman tells us the esophagoscopy, including the removal of the specimen, required two minutes and fifteen seconds. This case is instructive in connection with the preceding case. Both of these patients presented the same symptoms—difficulty in swallowing and regurgitation of food. Both had been, at one time, considered as having stomach trouble

¹ The esophagoscopic appearances are illustrated in Plate 1. A histologic report subsequently received from the Pepper Laboratory is: "Squamous-celled epithelioma."

without the presence of an esophageal lesion being suspected. The quickest and most certain way of diagnosing esophageal disease is by direct inspection with the esophagoscope. Esophagoscopy is a procedure that, once the knack is acquired, needs no anesthetic and requires but a few minutes. It almost invariably establishes the diagnosis and should be resorted to in every patient complaining of the slightest abnormality in swallowing. A thorough Roentgen-ray study should always be made before esophagoscopy, as the roentgenologist can give much information that the esophagoscope cannot; and I have found that in many cases esophagoscopy serves only to confirm the roentgenologist's opinion.

Croupy Cough and Dyspnea Simulating Diphtheria Due to Infective Tracheobronchitis.—This child, two years of age, was taken suddenly with a slight chill, fever, and croupy cough. Antitoxin was given. Cultures and smears being continuously negative, no membrane appearing in the fauces, and the child not improving, I am asked to inspect the larynx. Without any anesthesia, general or local, I elevate the epiglottis with the direct laryngoscope and look directly at the larynx and through the glottis down into the trachea. The subglottic tissues are swollen until they nearly meet in the middle line (see color plate), which is the condition that gives the croupy cough in diphtheria; but, there is no membrane. In the trachea moss-agate pus is visible. Contrasted with the endoscopic appearances of diphtheria there need be no hesitation in pronouncing this case one of infective laryngotracheobronchitis which is epidemic here in Philadelphia at the present time.

One very important point demonstrated by this case is that the larynx of any child can be directly inspected by the direct laryngoscope without any anesthetic, general or local, and without any more distress to the child than palpation for adenoids. Mirror laryngoscopy in a child of this age is impossible, and therefore it has been customary to make a guesswork diagnosis of a croupy cough and to give antitoxin any way. No fault can be found with the giving of antitoxin on a tentative diagnosis of diphtheria; it is perfectly justifiable to do so; but the time has

come when it should be known that the larynx of any child can be inspected by direct laryngoscopy, and the presence or absence of diphtheria determined.

Papilloma of the Larynx Simulating Diphtheria.—Here we have another case in which antitoxin was given for supposed diphtheria because it was not realized the larynx could be examined. This child was very croupy and dyspneic, with a moderate temperature. She had had what was supposed to be a chronic laryngitis accounting for hoarseness for some months before the croupy attack, but the severe croupy symptoms were sufficiently sudden and intense to justify the inferential diagnosis of diphtheria. After a month had elapsed with no improvement some misgivings as to the correctness of the diagnosis began to arise and the child was referred to the Bronchoscopic Clinic for diagnosis. On direct laryngoscopy the larynx was seen to be filled with multiple papillomata (see color plate). Doubtless the apparent suddenness of the croupy onset was due to intercurrent laryngotracheitis; the papillomata must have been in the larynx for many months. I removed the growths superficially without any trauma to the normal cords. Papillomata do not infiltrate the basal tissues, and it is a great mistake to ruin the voice by radical removal of the basal tissues. They repullulate on the surface and appear at new locations, but they do not infiltrate the deeper tissues. This is well illustrated in this patient by these beautiful and typical papillomata on the pillar of the fauces (see color plate). Of what use can it be to ruin the larynx by radical removal or radium burns when "recurrences" or, rather, new papillomata can appear at so remote a location as the pillar of the fauces? Moreover, the conditions here are very different from cancer. In cancer we have a progressive, infiltrative, fatal fungation, never fatal unless by mechanical occlusion of the airway, an easily avoided contingency; and, moreover, *papillomata of the larynx constitute a benign, self-limited disease*. Gentle laryngoscopic removals carefully done to avoid removal of any normal tissue, and repeated as often as necessary, will ultimately be followed by cessation of recurrences and the patient will have a good voice.

To illustrate this I present this other little patient who has been cured by direct laryngoscopic removal, and ask her to say "No." She does so, and you hear her loud, clear voice. When she first came to the Bronchoscopic Clinic she was aphonic and so dyspneic that she nearly asphyxiated every night.

CONTRIBUTION BY DR. WILLIAM G. SPILLER

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AËROCELE OF THE BRAIN

WHERE symptoms of subacutely developing intracranial pressure occur we think especially of tumor, abscess, hemorrhage, or meningitis, and where injury of the head has preceded the development of these symptoms our thoughts are directed more particularly to abscess, hemorrhage, or meningitis; and yet tumor may be latent and a trauma of the skull may occur a short time before the appearance of tumor symptoms. I have known large gliomas of the brain, latent for a long time, to develop a very rapid course and terminate fatally within a few weeks after the appearance of the first symptoms of intracranial disorder. To the lesions mentioned we must add aërocele of the brain, possibly confined to the cerebrum, certainly much more common in the cerebrum, developing after fracture of the skull. This lesion has been recognized only comparatively recently and the cases in literature are not very numerous, therefore it has seemed well to me to give a brief review of them with a discussion of their findings. They seem to be confined to the American and French literature, and yet I am convinced that after attention is directed more to the occurrence of this condition the cases will become much more numerous.

The air forms a distinct cyst in the brain. In the cases I have collected the lesion has been in the frontal lobe in almost all—there is only one exception to this in Imboden's case—usually with fracture implicating the frontal sinuses, and it appears that blowing the nose or sneezing causes the forcing of air through a fracture of bone communicating with air sinuses. In only one reported case was the collection of air in the ventri-

cles without an aërocele in the brain substance (Luckett and Stewart). It is questionable whether air from a fracture would find its way into the ventricles through the foramina of the brain when the brain is intact, but air does enter the brain through these foramina when admitted by lumbar puncture. If an opening were made by softening of brain tissue, such as might occur at the base of the brain from occlusion of blood-vessels or hemorrhage following fracture, air might readily penetrate this softened tissue and enter the ventricles. In the case reported by Luckett and Stewart separately a laceration was found at the base of the frontal lobe, through which the air may have entered the anterior horn of the lateral ventricle. Such a laceration was also present in my case.

The air does not form a cyst, as a rule, shortly after the occurrence of the fracture, although in one case (Holmes) air within the cranium was recognized within an hour after the fracture. More commonly a few weeks elapse before the aërocele is detected by the Roentgen rays, and the patient may be dismissed from the hospital so much improved as to make longer detention unnecessary, and be readmitted after a recrudescence. The great danger is meningitis, as bacteria may be carried with the air into the cranial cavity, and this seems to have been the usual cause of death, but escape from meningitis is possible as shown by the case of Glénard and Aimard, in which no meningitis was found at the necropsy after death from influenza about six months after the injury. If there had been any meningitis at an early stage it had entirely disappeared.

This case also demonstrated that the air could be absorbed and the space occupied by fluid. It is possible that the absence of meningitis in this case may be explained by the drainage of cerebrospinal fluid through a wound in the temporal fossa for two months, and when this wound healed, by drainage through the nose. Free discharge of cerebrospinal fluid in this way possibly may carry bacteria from the cranial cavity.

Death occurred in most of the cases. In Potter's case it is implied that recovery occurred. In this case and in that of Glénard and Aimard, with recovery, operation was not per-

formed, and in both the air was replaced by fluid. It is not permissible to conclude from this that operation is contraindicated, but it is noteworthy that in the other cases in which operation was performed with rare exception death occurred, and apparently from meningitis, but operation usually was late. Exposure of the brain in operation may be of great service, even producing cure, in the treatment of meningitis, possibly by relieving intracranial pressure. In association with Dr. Shields and Dr. Martin¹ I had the opportunity in 1909 to observe a case in which purulent meningitis was found at operation to be confined to a limited area of the motor region of the cerebral cortex. Following this exposure by operation complete recovery occurred and the patient is still living and is well.

The question of operation is a difficult one. If it is to be performed early it will be before any evidence of aërocele exists, and will be done in the hope of preventing this lesion. It is not customary to operate on every case of linear fracture of the skull without displacement of fractured bone and without signs of intracranial pressure, and it seems questionable whether operation would be advisable wherever the Roentgen rays show a linear fracture permitting communication with air sinuses. In some instances it is difficult or impossible to be certain from Roentgen ray examination whether an air communication with the interior of the cranium has been established. Presumably where such communication is shown by Roentgen ray plates taken shortly after fracture has occurred operation might make closure of this communication possible and thus prevent the development of an aërocele, and the possibility of the development of an aërocele must be considered in every case of fracture of the bones about the nose. It would be difficult to prevent the patient from blowing the nose and sneezing where such fracture exists, but something might be attempted in this direction to lessen the danger.

The diagnosis of aërocele should not be difficult. The change in the level of the fluid according to the position of the head is

¹ Shields, Spiller, and Martin, University of Pennsylvania Medical Bulletin, December, 1909, p. 298.

readily recognized by the Roentgen rays, and the splashing of the fluid from a sudden jarring of the head, such as occurs when a carafe partly filled with fluid is shaken, may be audible to the patient and bystanders.

It would seem that softening or hemorrhage occurs in the frontal lobe, and with the absorption of this degenerated tissue the space for a collection of air in the cerebrum is afforded, then the forcing of air into the cranial cavity completes the picture. Only one other case than the one I report seems to have been with microscopic examination, viz., the case of Glénard and Aimard. In this the cavity was lined by a membrane resembling the ependyma, but no such membrane was found in my case. In the latter softening of the base of the frontal lobe rendered access into the brain possible. The cavity produced by the air has a sharply defined, smooth wall with an uneven surface. In my case there was no indication of a new membrane and the wall was composed of somewhat denser than normal glia tissue. Medullated fibers were present, but were in a state of partial degeneration. It is doubtful whether air could produce a cyst in normal brain tissue, and the *aërocele* probably represents the extent of destroyed softened tissue. It is also doubtful whether an air cyst of the brain produced in this way really enlarges when once fully formed; indeed, in the case of Potter and in that of Glénard and Aimard the air was absorbed and its place taken by fluid. This may have some bearing upon the question of operation.

It is unfortunate that different designations have been employed for this lesion, as a search of the literature is thus rendered difficult. The condition has been described as *aërocele* of the brain, *hydropneumatocele* of the head, and *hydropneumocranium*.

Potter has suggested that air insufflated into the cranial cavity, following fracture through pneumatic sinuses, could easily play an important rôle in the formation of certain traumatic cysts in other parts of the brain than the frontal lobe, either filled with cerebrospinal fluid alone or mixed with hematic elements. He would expect symptoms to arise from

such cysts more often when in relation to the mastoid than to the frontal sinuses, but the evidence in the literature does not seem to me to justify this assumption. Whether air can be forced more readily from the mastoid region into the cranial cavity than from the frontal sinuses seems doubtful. The suggestion made by Potter is worthy of attention, and it may explain certain cyst formations which now are obscure.

The cases reported in the literature, so far as I have been able to discover them, are the following:

Luckett¹ regarded his case as the first on record of air in the ventricles of the brain diagnosed as such before operation, found to be so at operation, and lastly, proved to be correct at necropsy.

W. H. Stewart's² case is reported as one of air in the ventricles. It is the case published by W. H. Luckett. As a result of trauma the vertical plate of the frontal bone was fractured in the region of the outer edge of the right frontal sinus. The symptoms steadily improved, operative intervention was postponed, and in less than a fortnight the man demanded release from the hospital, and was allowed to leave. The accident was on November 24, 1912, and on December 12th the man was readmitted to the hospital with very severe headache, with occasional vomiting, and he was dull and listless, not taking any notice of his surroundings, would not converse with anyone, but seemed to understand thoroughly what was said and apparently read the papers intelligently. He was supposed to have abscess of the brain, and he had bilateral optic neuritis. On December 13th the Roentgen-ray examination showed that the cerebral ventricles were distended with air or gas. This had not been observed previously. Right-sided decompression was done, no fluid escaped when the dura was incised, and no mention is made of escape of air through this opening. A needle was then passed into the anterior horn of the lateral ventricle; the removal of the trocar was followed by two or three

¹ Luckett, Surg., Gyn., and Obstet., August, 1913, vol. 17, No. 2, p. 237.

² W. H. Stewart, American Journal of Roentgenology, vols. i and ii, December, 1913, p. 83.

quick spits of air and fluid, and then by clear cerebrospinal fluid. Because of meningitis, the large quantity of fluid, and the presence of air it was decided to drain the latter. A suboccipital operation was performed, the cisterna magna was opened, and considerable fluid mixed with bubbles of air escaped. On the fourth day after operation the temperature rose suddenly to 107° F. and death occurred. At the necropsy a laceration was found at the base of the frontal lobe, showing a communication with the anterior horn of the lateral ventricle. It was subsequently learned that a severe pain in the head, with a free discharge of clear fluid from the nose, followed a violent blowing of the nose, and it was believed that the patient had established a communication between the nose through the right frontal sinus and anterior lobe of the brain into the right lateral ventricle; and that when he blew his nose he also blew up the ventricles of his brain. There is no report of microscopic study of this brain. A recent suppurative meningitis was present. It is not known whether there was an aërocele before the ventricles became distended.

E. H. Skinner's¹ patient had a fracture of the right supra-orbital ridge of the skull, and although he had apparently recovered he had severe persistent headache and dizziness. Roentgen negatives showed a round area of increased transparency in the anterior part of the cranial cavity on the right side. The fracture was seen to extend into and through the posterior wall of the frontal sinus. He describes the finding of an air- or gas-bubble about the size of an egg in the anterior part of the right frontal lobe. The skull was trephined over the air tumor and the escaping air was collected under water. There was no inflammatory reaction visible. The patient left the hospital in good condition at the end of ten days, but twenty days after the operation he developed a severe headache, temperature became 104° F., pulse ranged from 130 to 140, he vomited, and became unconscious. He died the following day. Necropsy revealed leptomeningitis with a large amount of pus at the base of the brain.

¹ E. H. Skinner, *Jour. Amer. Med. Assoc.*, March 25, 1916, vol. lxvi, p. 954.

G. Cotte¹ reported a hydropneumatocele of the head in the frontal region following fracture of the skull. It was supposed to come from the frontal sinus. He considered it advisable to expose the tumor and to attempt to obliterate the communication with the frontal sinus, but this was not done. The final result in this case is not given.

G. W. Holmes² case was without examination of the brain apparently at operation or necropsy. He refers to a case of Walter J. Dodd of air in the ventricles which followed a fracture of the skull, but as it is stated that this case had not been reported, it is impossible to make further use of it. Holmes states that in those cases in which air was in the ventricles the orbital plate also was fractured. In the cases of aërocele the fracture was through the inner as well as the outer table of the frontal sinus.

In Holmes' case the Roentgen-ray examination made almost immediately after the accident showed a linear fracture through the outer table of the frontal bone and a suggestion of a continuation of the fracture through the inner table. The frontal sinus was involved. In one plate there was a large oval area of markedly diminished density in the frontal region. The outline of the area was irregular and it was not seen in the plate taken from the other side. For this reason it was thought at the time to be an artefact. This finding would appear to be a very early one of air within the cranium, although it was not recognized as such at the time.

The patient developed meningeal symptoms a week later, and from other plates made then a definite diagnosis of intracranial aërocele was made. At the operation a small crack was found in the middle of the anterior wall of the frontal sinus. The dura beneath the posterior wall of the sinus was incised and there escaped through the opening about 2 ounces of turbid serum and air. The patient died two days after the operation from meningitis. All that is said regarding the necropsy is that

¹ Cotte, *Bulletins et Mémoires de la Société de Chirurgie de Paris*, vol. xliii, 1917, p. 865.

² Holmes, *American Journal of Roentgenology*, vol. v, 1918, p. 384.

at the necropsy the surgical diagnosis and the Roentgen-ray findings were confirmed.

An important feature in this case was the finding of air within the cranium in plates taken within an hour after the accident. Holmes thinks that had this been recognized and immediate operation performed, the meningitis which developed later might have been prevented. He makes the wise suggestion that it is important to obtain careful roentgenographic examinations of all cases of fracture of the frontal bone immediately after the injury and also before the patients are discharged from the hospital, and in the interpretation of the roentgenogram especial attention should be given any areas of diminished density in the frontal areas.

Hollis E. Potter¹ speaks of his case as one of hydropneumocranium with air in the ventricles. A man, after a fall of 15 feet, probably had a fracture of the skull, but no loss of consciousness and no more pronounced nervous symptoms than a bitemporal headache which lasted only a week. He had some slight dizziness and a little positional discomfort, particularly on bending the head forward. He convalesced rapidly. Routine Roentgen-ray examination disclosed a frontal skull fracture, centering about the right supra-orbital arch, and involving both the internal and external walls of the frontal sinus and the orbital plate. Inside the cranium at the site of fracture there was evidence of gaseous accumulation, in volume and shape comparable to a small hen's egg. This was considered startling, as the symptoms of head injury had not been intense. This finding was not made until nearly three weeks after the injury. In the absence of signs of hemorrhage, infection, or intracranial pressure it was decided not to operate. After two weeks there was considerable increase in the volume of the subdural gas collection and the lateral ventricle was also partially filled with gas. The cavity was found now to contain fluid, the level of which varied with the position of the head, and under the screen the fluid could be seen to splash with any sudden movement of the head, and the splashing was audible.

¹ Hollis E. Potter, *American Journal of Roentgenology*, vol. vi, 1919, p. 12.

From this time on the air disappeared, whether by absorption or expulsion is not certain, so that the screen and plate records of July 25th showed no evidence whatever of the cavity. The accident had occurred on May 20, 1918. While it is not clearly so stated, it is implied that the man made a complete recovery from his head injury.

Potter says that while cases of recognized intracranial air are extremely rare in the literature, it is probable that many cases of intracranial air collections are overlooked because of the infrequency of Roentgen-ray examination two or three weeks after the injury, where pneumatic sinuses are opened by fracture. He says also that before the days of the Roentgen ray reports of intracranial emphysema and gaseous tumors of the brain are recorded as occurring even in the middle of the last century, but they are not very illuminating. He believes the air may have gained entrance to the ventricle from the air cyst by the round-about passage formed by the foramina of Magendie and Luschka, the fourth and third ventricles, and the foramina of Monro. His case affords no contribution to the pathology of air cyst formation, as no necropsy was obtained and there was no operation.

R. J. May's¹ case is very briefly reported as one showing air within the cranial cavity. The patient was knocked down and died within a few hours. Roentgenograms were made the next day, several hours after death. A fracture was found in the right frontal bone extending into the right frontal sinus. It is merely stated that a large air space was shown in the frontal region. There was no necropsy report.

The case reported by Glénard and Aimard² is as follows: A soldier was shot in the head, the bullet entered a little to the left of the middle of the forehead, leaving a small wound, and had its exit at the left temporal fossa, leaving a large opening from which blood and cerebral tissue escaped. Cerebrospinal fluid drained from this wound in small quantity for two months, and when the wound healed the fluid escaped by the nose. A Roent-

¹ R. J. May, *Amer. Jour. of Roentgen.*, vol. vi, 1919, p. 190.

² Glénard and Aimard, *La Presse Médicale*, March 10, 1919, p. 123.

gen-ray picture taken two months after the injury showed a clear space in the left frontal lobe. The interpretation of the findings was that the loss of cerebral tissue caused a cavity in the frontal lobe which filled with air from a communication with the frontal sinuses.

The escape of cerebrospinal fluid by the nose continued about a month and then ceased entirely. It was then believed that the cavity partly filled with cerebrospinal fluid, as a bruit was recognized by the patient and any bystander when the man shook his head forcibly or bent it backward suddenly, and sounded like a carafe half-filled with water and shaken violently. The Roentgen-ray pictures taken at this period showed that the aërocele was smaller and that the upper level of the liquid which had encroached upon it was horizontal in any position of the head. The bruit later ceased entirely and the Roentgen-ray pictures no longer indicated the existence of an aërocele. The fluid was then believed to fill the entire cavity.

Death occurred from influenza approximately six months after the injury. There had been no cerebral complications. The man had had headache, but the symptoms were slight. There had been no impairment of motion, memory had been a little affected, but intelligence not impaired. Operation was not thought advisable.

At the necropsy the brain externally appeared normal, but was adherent at the third frontal convolution and anterior portion of the temporal lobe. When these adhesions were ruptured a liquid escaped which had filled a cavity of the left frontal lobe. The walls of this cavity were irregular and covered by a sort of connective-tissue membrane of new formation. A later report in this case was made by Barbe and Glénard.¹ The cyst lining resembled the ependymal lining. A zone of sclerosis was found beneath it in which were no medullated nerve-fibers. The lining membrane contained small vessels of new formation, but there were no signs of inflammation, no cellular infiltration, no diapedesis, no edema.

¹ Barbe and Glénard, *La Presse Médicale*, July 7, 1919, p. 376.

H. M. Imboden's¹ case was one of fracture of the skull, and several pieces of bone were removed. A shadow of diminished density was found later by Roentgen-ray examination in the upper portion of the cranium, which was believed by him to indicate displacement of the brain by air. This shadow was immediately beneath the site of fracture. No operative procedure was employed to permit the air to escape. A Roentgen examination about a month later showed the air completely displaced, apparently by brain tissue. The photographs show the shadow in the uppermost part of the cranium apparently remote from all air sinuses, and in this respect this case differs from all the others which I have collected.

In my case the diagnosis of aërocele was made by Dr. Alfred S. Doyle² when I sent the patient to the Department of Roentgenology of the University Hospital, and the case has been reported by Dr. Doyle with Roentgen-ray photographs. My notes, however, are given a little more in detail and I have been able to make a microscopic study of the brain.

A. G., aged fifty years, entered the University Hospital in my service August 30, 1919, when the following notes were taken:

He met with an automobile accident on June 7, 1919, and had his skull fractured in the left frontal region. He was unconscious after the accident for some days, and since that time he had complained of headache in the left frontal region. He had been blind in the left eye since the accident.

Two weeks ago he began to have frequent fainting spells, four or five daily. He became irrational a week ago, and if he were questioned about his farm he might answer something about a baseball game, or something else entirely foreign to the subject. He had not had vomiting. Dr. C. C. Wolferth stated he had known the patient about twenty years. Three or four days before the man came to the University Hospital he did not recognize Dr. Wolferth, but knew who he was when his name was

¹ Imboden, *American Atlas of Stereoroentgenology*, vol. xi.

² A. S. Doyle, *American Journal of Roentgenology*, vol. viii, No. 2, p. 73, 1921.

mentioned. Memory had failed in other respects, but he had been able to go from his farm in New Jersey to the Cooper Hospital in Camden alone, a distance of about 17 miles.

September 10, 1919 examined by Dr. A. H. Woods. He was found to have no ataxia on standing with eyes open or closed and gait was not ataxic. The left eyeball was sunken in the orbit and displaced somewhat downward. He had no facial weakness. The eyeballs were moved well, as was also the tongue. Voluntary movement was normal in the neck, trunk, and limbs. The tendon reflexes were prompt, especially the patellar. The plantar reflexes were normal. There was no clonus. Tactile sensation was normal everywhere. He had no motor and no sensory aphasia.

He was oriented as to time, place, and his existing circumstances. He gave the names and ages of his 9 children, the date and circumstances of his wife's death last June, he told correctly details of the war and matters of current history.

He was quiet after he entered the hospital, remained in bed, and never spoke unless addressed. Nurse and patients about him had noticed no peculiarities. He wet and soiled the bed, and said he could not call the orderly because he had no warning of sphincter release.

I referred this man to the Department of Roentgenology, and stereoscopic plates made by Dr. Doyle indicated a fracture running into the frontal sinus from the left temporal region, and Dr. Doyle diagnosed a collection of air in the left temporal region.

September 17th: The man got up in the night and wandered about the ward. This morning he showed signs of increased intracranial pressure. Pulse was slow and full and respiration irregular and stertorous.

September 8th: He could not be aroused from his stupor. Since yesterday he had shown irregular convulsive seizures involving the whole body and was decidedly spastic. The heart action was more feeble. Respiration was more irregular and labored. The face was becoming more cyanotic.

September 19th: He seemed brighter and replied that he

was better and said he had no pains. He soon dropped back into a stuporous condition, and had numerous convulsions.

I requested Dr. Muller to open the skull in order to allow the air to escape, to relieve pressure, and to lessen any lesion that might be present. Dr. Muller operated September 24th. He made a trephine opening through the left temporal region. The dura was tense, and when it was opened air rushed out with an audible hissing noise, but more air escaped at the necropsy, so that it could not all have been removed at the operation. Only slight hemorrhage occurred. The dura was closed and freed from the skull.

September 25th: Pulse. temperature, and respiration went up rapidly and the man died. Dr. F. A. Weidman made the necropsy, and very kindly handed over the brain to me. His report is as follows:

Between the operative wound and the dura there was a layer of clot about 8 mm. thick; also between the dura and the cerebral cortex there was an accumulation of about half this thickness. The dura was adherent under the line of the old fracture, the brain substance projected strongly upward here immediately under the surgical wound, and upon puncture a non-inflammable gas escaped. The air cyst appeared to be about the size of a small hen's egg. At the most anterior portion of the frontal lobe two small perforations were discovered which were close, on the one hand, to a cleft in the cribriform plate of the ethmoid at the right, and on the other, to a projecting shelf of fractured internal lamella on the left. A probe could be passed through the foramen into the nose. On chiseling away the shelf on the left air spaces of the sinus were at once encountered. The actual communication between the gas cyst and the nose could not surely be determined, inasmuch as the brain substance was lacerated as a result of sagging on account of its weight. The most likely mode of entrance appeared to have been through the cribriform plate of the ethmoid, inasmuch as this was much closer to the aperture first noted in the brain substance.

The bone of the roof of the orbit was strongly bulged toward the cranial cavity, and the internal lamella under the line of

fracture was porous, discolored grayish brown, and evidently nearly necrotic.

The anterior pole of the left temporal lobe was covered by slightly grayish tissue, and under it the convolutions were atrophic and flattened. The pituitary body was likewise reduced in size, being flattened upon the floor of the pituitary fossa, and of a slightly yellowish character. Elsewhere the brain surface appeared grossly normal.

Two sections were cut from the upper part of the air cyst in such a way as to include the whole thickness of its wall at this region, and show the pia-arachnoid on one side and the cyst lining on the other. In both sections the endothelial covering of the pia was accentuated by a hyperplasia of its cells to a narrow but dense hyaloid zone of closely placed cells whose nuclei were long and spindle form, and frequently clustered into groups of two or three. Two membranes of this sort could be traced, one of which might represent pia and the other arachnoid, and between them was a loose fibrous tissue which appeared to be of new and pathologic development, and derived alike from the internal and external membranes. There were no important inflammatory evidences here. At most but an isolated polymorphonuclear leukocyte could be discovered at wide spacings. In one section, however, the two membranes were separated more or less by extravasated masses of erythrocytes. The latter cells were for the most part, well preserved, but occasionally were fused and of a rusty, more or less hyaloid character. The cerebral substance, normal appearing in one section, was highly vacuolated in the other (the one showing the meningeal hemorrhage), along a zone adjacent to the cyst lining. There were again no important inflammatory signs, and only the slightest recognizable hyperplasia of glia-cells. The lining of the cyst was constituted directly by cerebral substance, there was no membrane, and no evidence of compression. Blood-vessels in all sections were fully distended by erythrocytes and occasionally contained small clumps of pink hyaline material. They showed no peripheral infiltrates. In sections stained by Gram's method no bacteria could be found.

Sections from a lower level of the cyst wall were examined by me and showed intense infiltration of the pia with polymorphonuclear cells, very different from the finding of Dr. Weidman in sections from a higher level, and therefore the meningitis was very limited. Perivascular infiltration of mononuclear cells was



Fig. 147.—Photograph of a horizontal section of the brain revealing the cyst in the left frontal lobe. The cyst extended only a little above this level.

seen within the brain substance. The sections colored by the Weigert hematoxylin method stained poorly and showed a considerable reduction in the number of medullated nerve-fibers. The glia near the cyst wall contained many small vacuoles and the glia-cells here were increased in number. The longest diameter of the cyst was 6 cm. extending along the frontal lobe

(Fig. 147), the anteroposterior diameter was 3 cm. A small clot of blood was found on the cyst floor. The cyst wall was about 2 mm. thick in its anterior portion. The base of the left frontal and left temporal lobes showed considerable sclerotic tissue, the result of former softening, and the cyst wall at the base of the frontal lobe was very thin and probably readily admitted air through this softened cerebral tissue.

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THE CLINICAL VALUE OF THE KOLMER MODIFICATION OF THE WASSERMANN TEST

THE Wassermann test is the most important biologic reaction employed in medicine. It is not a specific test in the accurate sense of the term, inasmuch as the antigens used are non-specific, and there is no union of a specific antigen with the antibody in the blood. Indeed, relatively little is known of the nature of the Wassermann reacting substance in the blood. It is not believed that it is an immunologic substance; it is possible that it is a product due to the action of the spirochete on body cells.

Neisser has aptly designated the reacting substance in the blood-serum "reagin," and in the interests of brevity and precision we shall employ this term.

Like all biologic tests, the Wassermann test has its limitations. Its great fallibility is in the negative outcome. To be sure, one occasionally encounters falsely positive tests, but with good laboratory technic they are extremely rare. False negatives, however, are excessively common and, unfortunately, they occur in the very cases in which we most need diagnostic support. It is rare to encounter a negative Wassermann

reaction in the presence of frank and extensive manifestations of syphilis. In these cases the serum reaction is not necessary to establish the diagnosis. It is in late circumscribed lesions or in cases of obscure visceral involvement that the Wassermann may be negative, and it is just in such conditions that we desire laboratory aid to fortify our clinical judgment. A negative outcome in these cases is prone to have the effect of persuading the clinician that his suspicion is not warranted, and the common result is that the patient is deprived of the possible advantages of antisyphilitic treatment.

We recall the cases of a young man of twenty-seven, of vigorous build and in apparently perfect health, who had an obstinate interstitial keratitis. Repeated negative Wassermans had convinced ophthalmologists that the case was not luetic. By exclusion it was, therefore, regarded as tuberculous. We gave him a provocative arsphenamin treatment and his Wassermann became moderately positive. Under further intravenous administration of the arsenical the keratitis was cured. We later learned that at the age of nine he had suffered from a keratitis which was cleared up by mercurial inunctions. In this case the negative Wassermann tests threw the patient's medical counsel off the track. Indeed, they might have treated him more wisely if the test had not been in existence. Cases of a similar character might be multiplied indefinitely.

Need of More Sensitive Test.—It was early recognized in the history of the Wassermann test that there was a tendency to the development of negative reactions in cases in which the history and the response to syphilitic treatment indicated that there should have been a positive Wassermann outcome. One of the most important steps in increasing the sensitivity of the test was the employment of cholesterol to fortify the antigens. When these were first introduced there was criticism in certain quarters that we were apt to produce false positive reactions and thus deceive the medical mind and sorely distress the patient. Experience has proved not only that, when properly checked, this modification has not led to this result, but that the cholesterolized antigens, although an advance, were never-

theless not sufficiently sensitive to detect small amounts of reagin in the blood of some syphilitics. Many technics have since been devised to increase the sensitiveness of the test and at the same time preserve the specificity of the complement fixation.

Unfortunate Result of False Negatives on the Conduct of Treatment.—Under modern treatment the obvious manifestations of syphilis disappear so rapidly that the only criterion remaining after a month or two is the serum reaction. The purpose of our therapeutic measures is to produce and maintain a negative Wassermann. Too often the physician even after a relatively brief course of treatment suspends his treatment because the Wassermann has become negative. He tells his patient "We will make another blood test in a month and see what the blood shows." By this unwise procedure much valuable time is lost, inasmuch as in most cases there will later develop a relapsing positive or a recurrence of some syphilitic manifestation. The patient is really worse off than in the pre-Wassermann and pre-arsphenamin days when he received three years of mercurial treatment. Patients must receive an *irreducible minimum* of treatment in early syphilis irrespective of the outcome of the Wassermann reaction. Many of these reactions are negative because of the present imperfection of the Wassermann technic. Possibly the technic ordinarily in use is only able to detect reagin when it is present in a given quantity. When in less quantities a more sensitive antigen and technic are required. We believe that our experience with the Kolmer method proves the above hypothesis to be the truth.

KOLMER'S NEW METHOD

The exhaustive investigations carried out by Kolmer¹ on the Wassermann test have resulted in the development of a technic which possesses a superior degree of sensitiveness to the methods previously in use. According to Kolmer² the test is

¹ Series of thirty-two papers being published in the American Journal of Syphilis, beginning March 1st (January, 1919).

² Kolmer, J. A.: Standardization of the Wassermann Reaction, Jour. Amer. Med. Assoc., 1921, 77, 776-779.

technically accurate and uniform, and, in addition, its performance is simple and economical.

Kolmer has indefatigably studied every phase of the complement-fixation test for syphilis. In this study he has devised many procedures for the performance of the Wassermann test in order to avoid pitfalls in technic, and, moreover, to increase the accuracy of the reaction. The following may be given as a brief summary of the technic of the test. The antigen employed¹ is new and is highly sensitive. It is used in relatively large amounts. The tested serum is used in relatively large and varying amounts, 0.1 c.c., 0.02 c.c., 0.004 c.c., 0.002 c.c., and 0.001 c.c. It is, therefore, a quantitative Wassermann reaction.

Method.—The serum is heated for only fifteen minutes instead of thirty in order to remove the possibility of false reactions with the least destruction of reagin. A mixture of guinea-pig complements is prepared in such a manner as to increase sensitiveness to fixation by the antigen and the syphilis reagin. The tested serum is mixed with the antigen for a brief period before the addition of complement. A primary incubation of eighteen hours in a refrigerator is followed by ten minutes in a water-bath. A daily titration of the complement in the presence of the antigen is carried out for the purpose of securing a close adjustment of the hemolytic system to a refrigerator primary incubation. The reaction is read within three hours after the conclusion of the secondary incubation with the aid of a reading scale.

We have studied the results of the Kolmer method of performing the Wassermann tests in a total of over 2000 tests. In all of these cases the older method of performing the Wassermann reaction with three antigens—namely, cholesterolized, alcoholic syphilitic liver, and acetone insoluble lipoids—was also performed. In addition, the reaction was studied on a number of non-syphilitics. In this latter study we have not obtained any positive reactions.

¹ A description of the new antigen will be given by Dr. Kolmer in a forthcoming publication.

As a result of the foregoing observations we regard the Kolmer modification of the Wassermann test as a highly sensitive one. It is more sensitive than the commonly employed methods of conducting the test. A most important consideration is that we have no reason to believe that the test yields false positive results. In a comparison of the two methods we have observed that the Kolmer technic is the first to give positive and the last to yield a negative reaction and, again, the first to detect recurrent positive reactions.

In primary syphilis we have noted that the Wassermann reaction with the Kolmer method tends to appear earlier than with the older method. In early primary syphilis the reaction first appears positive in the lowest dilution—0.1 c.c. of serum; the development of a positive reaction in the remaining dilutions (0.02, 0.004, 0.002, and 0.001 c.c.) of serum varies according to the duration of the chancre (Cases 1-3). Just before and at the time of appearance of the secondary eruption a 4+ reaction is obtained almost uniformly in all dilutions of the test (Cases 2, 4).

In tertiary syphilitics with active manifestations of the disease many patients give a positive reaction in all dilutions (Cases 5-9). In those without active manifestations (latent or asymptomatic) the reaction may or may not be 4+ in the highest dilution (Cases 10-14). In these instances the reaction with the old method may be 4+ in all antigens, no matter whether the quantitative method of Kolmer is 4+ in all dilutions or only in the lowest dilutions of serum employed. The quantitative method of Kolmer in the foregoing type of syphilitics is of aid in determining, at least serologically, the status of the infection. The patients with a 4+ reaction in all dilutions of serum employed are doubtless expressions of a greater degree of syphilitic infection than is present in those in whose serum a 4+ reaction is obtained only in 0.1 c.c. or in 0.02 c.c. and the remaining dilutions negative. Moreover, one can forecast that less treatment will be required to render the reaction entirely negative in the cases in which the reaction is

not positive in all dilutions than is required in the cases where the reaction is 4+ in all dilutions.

The quantitative reaction in many congenital syphilitics, particularly in those with active manifestations, is 4+ in most of the dilutions (Cases 15, 16). Here, again, we have noted that cases with a 4+, or weaker reaction, only in the lowest dilution becomes negative with less treatment than do cases in which a positive reaction is obtained in all the dilutions.

The Kolmer technic of performing the Wassermann reaction in a quantitative way is of particular value as a criterion of the effectiveness of antisyphilitic treatment. After such treatment the positive reactions in the highest dilution is the first to disappear, followed by changes in the next highest dilution (see Cases 17-19). As will be seen in the case histories herein reported the amount of antisyphilitic treatment required to effect a reversal of a positive Wassermann test in any one dilution of the test is very variable.

With the older method of performing the Wassermann test we have noted what is already well known, namely, that the test performed with a cholesterolized antigen is most sensitive, the next most sensitive antigen is one composed of acetone-insoluble lipoids, and the least sensitive antigens are alcoholic extracts of syphilitic liver. A 4+ reaction in all the dilutions of the Kolmer method nearly always yields with the same specimen a similar reaction with the three above-named antigens when the test is performed by the older method.

However, as is seen in Cases 15, 16, 12, a negative reaction may be present in the highest dilution of the Kolmer technic, yet a 4+ reaction is obtained with the three antigens used in the old method. When less than a 4+ reaction is obtained in the old method one usually observes a negative reaction, in the dilution of 0.001 and 0.002, and usually less than 4+ in the dilution of 0.004.

When a decrease in the complement fixation occurs by the older method it usually appears first in the least sensitive antigen, namely, alcoholic extracts of syphilitic liver. A subsequent weakening is next seen with the antigen composed of an extract

of acetone-insoluble lipoids. A further weakening is finally observed in the most sensitive antigen, namely, the cholesterolized one. In this way a Wassermann test performed with these three antigens is in a way a quantitative one. It will be readily seen, however, in a comparison of the results of the two methods of performing the Wassermann test as given in the case histories that such a quantitative interpretation of the Wassermann when performed with three antigens is not nearly as accurate as the method of performing the test with graded dilutions such as is employed in the Kolmer method.

The quantitative Wassermann, in addition to its value in determining the effectiveness of antisyphilitic treatment, has an added value in interpreting another condition. We have noted not infrequently that certain tertiary syphilitics after treatment with the arsphenamins, paradoxical as it may seem, are influenced in such a manner as to cause a positive reaction to remain stationary. At all events we have noted in some cases (Cases 20, 21) a relatively prompt appearance of a negative reaction after the cessation of treatment with the arsphenamins. In these instances the positive reaction persisted and was of the "Wassermann fast" type during the time treatment with the arsphenamins was administered. The foregoing course of events may be suspected by the quantitative Wassermann when after treatment a positive reaction appears and persists in the higher dilutions of the test in which dilutions the reaction was negative prior to treatment (Case 22).

In Cases 23-27 it will be seen that the usual Wassermann test had become negative as the result of antisyphilitic treatment, but with the Kolmer method it was still positive. This difference is not infrequently noted after treatment, particularly in patients in whom the infection has existed for a number of years and the previously positive Wassermann reaction had been of long duration. Whereas, in patients in the relatively early stages of syphilis, as a result of treatment negative reactions with each of the methods appear at about the same time.

It will be noted in Case 28 that as the result of treatment positive reactions with both methods became negative. Some

time after the cessation of treatment, however, the Kolmer method yielded a positive reaction. This has been a frequent observation and forecasts the later appearance of a recurrent positive reaction with the old method. There are two interpretations of a negative Wassermann in cases in which the reaction in a known syphilitic subsequently becomes positive.

Either the Wassermann test is not sufficiently sensitive or delicate to detect the presence of those substances which give rise to it or, there is an actual disappearance of these substances from the serum of the syphilitic. In the present state of our knowledge we do not know which interpretation is correct. At all events the foregoing type of case shows that the Kolmer method is more sensitive in detecting the presence of the Wassermann-producing substance than the usual method of performing the test.

PRIMARY SYPHILIS

Case 1.—J. H. Male, aged twenty-three.

Chancre of the lip, duration three weeks.

Dark-field examination positive.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 ¹ 3+
0.02 c.c. 4+	Antigen No. 2 1+
0.004 c.c. 2+	Antigen No. 3 2+
0.002 c.c. 1+	
0.001 c.c. —	

Comment.—A three-week chancre here shows a stronger reaction with the new technic than with the old method.

Case 2.—M. F. Female, aged twenty.

Typical chancre on lower lip. Duration seven weeks.

No secondary eruption. Dark field positive.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 4+	Antigen No. 3 4+
0.002 c.c. 4+	
0.001 c.c. 3+	

¹ Antigen No. 1 cholesterolized.

Antigen No. 2 alcoholic syphilitic liver.

Antigen No. 3 acetone insoluble lipoids.

Comment.—After seven weeks both tests are so strongly positive that there is little differentiation.

Case 3.—A. Female, aged nineteen.

A chancre on labium majorum. Duration four weeks.

Dark field positive.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 2+	Antigen No. 3 4+
0.002 c.c. 1+	
0.001 c.c. —	

Comment.—In this patient a four-week-old chancre does not show 100 per cent. complement fixation in the higher dilutions.

SECONDARY SYPHILIS

Case 4.—C. H. Secondary eruption of three weeks' duration. Healed chancre on penis untreated.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 4+	Antigen No. 3 4+
0.002 c.c. 4+	
0.001 c.c. 4+	

The reaction of the patient's wife, who also presented a secondary eruption of syphilis, was:

<i>Kolmer technic.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 4+	Antigen No. 3 4+
0.002 c.c. 4+	
0.001 c.c. 4+	

Comment.—In these cases the older method and the Kolmer method both yield 100 per cent. fixation, but the latter will show the influence of treatment more readily because the higher dilutions of the patient's serum will become negative earlier than the reactions by the usual method.

ACTIVE TERTIARY SYPHILIS

Case 5.—B. S. Male, aged fifty-two.

Infected twenty years ago. No previous treatment. Clinical examination—aneurysm.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 1+	Antigen No. 3 4+
0.002 c.c. —	
0.001 c.c. —	

Two weeks later, during which time he received two injections of neo-arsphenamin, the Wassermann reaction was as follows:

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 3+	Antigen No. 3 4+
0.002 c.c. 2+	
0.001 c.c. 1+	

Comment.—The greater elasticity of the Kolmer technic is here shown. The old test suggests 100 per cent. fixation of complement, but the newer method indicates that this is not the case. Two injections of neo-arsphenamin appear to have caused some provocative influence on the reaction, for it was somewhat stronger after these injections than before, although the older method does not indicate any change.

Case 6.—C. S. Age thirty-five.

Denies infection and previous treatment; at present has an ulcerating nodular syphilid involving forehead.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 4+	Antigen No. 3 4+
0.002 c.c. 3+	
0.001 c.c. 1+	

Comment.—As in Case 5, a finer differentiation in the reaction is shown by the new method.

Case 7.—M. T. Female, aged twenty-six.

Presents a nodular syphilid on forehead. No previous treatment.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 3+
0.004 c.c. 4+	Antigen No. 3 4+
0.002 c.c. 1+	
0.001 c.c. —	

Comment.—In this tertiary case both reactions are about equal in strength, but the graded quantitative method gives more information as to the amount of "reagin" in the blood.

Case 8.—L. Male, aged forty.

History of infection twenty-five years ago. Has had no previous treatment. At present presents a tertiary squamous syphilid of the palm.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 =
0.02 c.c. 1+	Antigen No. 2 —
0.004 c.c. —	Antigen No. 3 —
0.002 c.c. —	
0.001 c.c. —	

Comment.—The value of the new test is here impressive and important. The patient had an eczematoid looking eruption on the palm which was suspected of being luetic. Had the old method only been employed the plus-minus reaction would have left one in doubt. The reaction by the new method is a strong enough positive to persuade one to the definite view of the luetic character of the eruption.

Case 9.—Dr. X. Aged forty.

No history of lues. Severe chronic glossitis with superficial ulcerations. A clinical diagnosis of "glossitis syphilitica chronica" was made despite the report of a recent negative Wassermann made in another city. The Wassermann test subsequently made by Dr. Kolmer was as follows:

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 2+
0.02 c.c. 3+	Antigen No. 2 —
0.004 c.c. —	Antigen No. 3 =
0.002 c.c. —	
0.001 c.c. —	

Comment.—The old method gave a weakly positive and the new method a strongly positive reaction. The latter gives one greater assurance of the correctness of the clinical diagnosis and justifies specific treatment.

LATENT ASYMPTOMATIC SYPHILIS

Case 10.—W. S. Male, aged thirty-two.

Infected six years ago. During past two years has had seven injections of arsphenamin and one hundred injections of mercury. At present is clinically negative.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Chol. 4+
0.02 c.c. 4+	Alch. 4+
0.004 c.c. —	Acet. 4+
0.002 c.c. —	
0.001 c.c. —	

Comment.—The reaction by the old method might lead one to suspect a Wassermann fast condition, but the negatives, with the higher dilution of serum in the new test, suggests that this is not the case.

Case 11.—S. R. Male, aged fifty-one.

Infected thirty years ago, no previous treatment.

Complained of pain in chest, cardiovascular examination was negative.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 3+	Antigen No. 2 4+
0.004 c.c. —	Antigen No. 3 4+
0.002 c.c. —	
0.001 c.c. —	

Comment.—The old test suggests complete complement fixation, but the greater differential delicacy of the new test shows that there is less "reagin" in the blood than would have otherwise been believed.

Case 12.—R. P. Male, aged thirty.

This patient denies infection and previous treatment. He has no complaint. He was referred for treatment because his

physician found a 4+ Wassermann reaction taken in the course of a general physical examination. He was entirely negative clinically except for irregular pupils which reacted very sluggishly to light.

Kolmer method.

0.1 c.c.	4+
0.02 c.c.	4+
0.004 c.c.	2+
0.002 c.c.	—
0.001 c.c.	—

Old method.

Antigen No. 1	3+
Antigen No. 2	1+
Antigen No. 3	1+

Comment.—While the new method shows a stronger reaction than the old, it does not shed any superior degree of illumination upon the case.

Case 13.—P. H. Male, aged thirty.

Infected ten years ago, at which time he received two injections of arsphenamin, no other treatment since. Has no complaint. Pupils are irregular and react sluggishly to light.

Kolmer method.

0.1 c.c.	4+
0.02 c.c.	4+
0.004 c.c.	4+
0.002 c.c.	3+
0.001 c.c.	—

Old method.

Antigen No. 1	4+
Antigen No. 2	4+
Antigen No. 3	4+

Comment.—Another illustration of a finer differentiation of the reaction in a case of neurosyphilis.

Case 14.—P. M. Male, aged twenty-eight.

Denies infection; married; wife has had 2 miscarriages and 2 children born dead.

Is clinically negative except irregular pupils, which react sluggishly.

Kolmer method.

0.1 c.c.	4+
0.2 c.c.	4+
0.004 c.c.	4+
0.002 c.c.	3+
0.001 c.c.	—

Old method.

Antigen No. 1	4+
Antigen No. 2	3+
Antigen No. 3	4+

Comment.—The two reactions run closely parallel.

CONGENITAL SYPHILIS

Case 15.—R. McG. Aged seven.

Father is tabetic. Mother has 4+ W. R.

No subjective or objective symptoms. The patient is ill nourished, has Hutchinson teeth. History of having had interstitial keratitis. At the time the following Wassermann tests were made twenty-three injections of neo-arsphenamin injections were previously administered.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 4+	Antigen No. 3 4+
0.002 c.c. 2+	
0.001 c.c. —	

Comment.—Many cases of congenital lues have resistant Wassermanns. The new test suggests that more impression has been made by treatment than is indicated by the old test.

Case 16.—H. Di C. Aged eight.

Father has 4+ reaction. Mother's reaction is negative. The patient is clinically negative. At the time the Wassermann reaction was made the patient received five injections of neo-arsphenamin.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.2 c.c. 4+	Antigen No. 2 4+
0.004 c.c. —	Antigen No. 3 4+
0.002 c.c. —	
0.001 c.c. —	

Comment.—The old technic gives the same degree of complement fixation as is seen in early secondary syphilis. The new test indicates that this is not strictly true.

FEATURE OF THE KOLMER TECHNIC

Case 17.—E. J. Female, aged forty-six.

Probably infected eighteen years ago. No previous treatment. At present gumma involving hard palate.

Kolmer method.

0.1 c.c.	4+
0.2 c.c.	4+
0.004 c.c.	4+
0.002 c.c.	4+
0.001 c.c.	4+

Old method.

Antigen No. 1	4+
Antigen No. 2	4+
Antigen No. 3	4+

After treatment there was a gradual disappearance of the positive reaction with the Kolmer technic, in the highest dilution of serum. Whereas the reaction remained 4+ with the old method. After twenty-three injections of neo-arsphenamin the reaction was as follows:

Kolmer method.

0.1 c.c.	4+
0.02 c.c.	4+
0.004 c.c.	4+
0.002 c.c.	—
0.001 c.c.	—

Old method.

Antigen No. 1	4+
Antigen No. 2	4+
Antigen No. 3	4+

Comment.—An old case of syphilis with a Wassermann difficult to reverse. The old test shows no serologic improvement, but the finer technic of the new method demonstrates that, as a matter of fact, there has been some serologic improvement.

Case 18.—J. K. Female, aged forty. Married.

Denies infection and previous treatment. Presents nodular tertiary syphilid involving face.

Kolmer method.

0.1 c.c.	4+
0.02 c.c.	4+
0.004 c.c.	4+
0.002 c.c.	4+
0.001 c.c.	3+

Old method.

Antigen No. 1	4+
Antigen No. 2	4+
Antigen No. 3	4+

After ten injections of neo-arsphenamin and mercury by mouth administered in the course of the following eight months the reaction was:

Kolmer method.

0.1 c.c.	4+
0.02 c.c.	3+
0.004 c.c.	—
0.002 c.c.	—
0.001 c.c.	—

Old method.

Antigen No. 1	2+
Antigen No. 2	1+
Antigen No. 3	1+

Comment.—In this case improvement in the serum reaction is evident in both tests, but the new test exhibits a stronger reaction.

Case 19.—H. F. Female, aged twenty-five.

Infected two years ago, since which time the patient received twelve injections of neo-arsphenamin. Clinical examination is entirely negative.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 3+	Antigen No. 3 4+
0.002 c.c. 1+	
0.001 c.c. —	

After ten injections of neo-arsphenamin administered at weekly intervals:

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. —	Antigen No. 3 4+
0.002 c.c. —	
0.001 c.c. —	

After twenty injections of neo-arsphenamin administered at weekly intervals:

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 2+	Antigen No. 3 4+
0.002 c.c. —	
0.001 c.c. —	

Comment.—Again the greater delicacy of the new technic is evident. The old test discloses no serologic improvement, whereas such has actually taken place.

THE PROVOCATIVE INFLUENCE OF TREATMENT

Case 20.—H. W. Female, aged twenty-four.

Denies infection and previous treatment; no complaint.

Wassermann reaction taken because she apparently infected, by sexual relations, another person. Complete physical examination negative.

Kolmer method.
Not performed.

Old method.
Antigen No. 1 4+
Antigen No. 2 4+
Antigen No. 3 4+

After thirty-seven intravenous injections of neo-arsphenamin the reaction was:

Kolmer method.
0.1 c.c. 4+
0.02 c.c. 4+
0.004 c.c. —
0.002 c.c. —
0.001 c.c. —

Old method.
Antigen No. 1 4+
Antigen No. 2 4+
Antigen No. 3 4+

Neo-arsphenamin was purposely stopped and intramuscular injections of mercury administered. After ten injections of 1 grain of mercury salicylate the following reactions were obtained:

Kolmer method.
0.1 c.c. 2+
0.02 c.c. —
0.004 c.c. —
0.002 c.c. —
0.001 c.c. —

Old method.
Antigen No. 1 =
Antigen No. 2 —
Antigen No. 3 —

Comment.—A latent case with a resistant Wassermann. The greater influence of the new test is shown in the earlier improvement in the reaction, and second, in being later to become effaced.

Case 21.—K. Female, aged twenty-eight.

Chancre of the lip in 1911. Treatment consisted of mercury administered at regular intervals until February, 1919, at which time the patient first came under our care. At this time clinical examination showed a pronounced cachexia and weakness.

The following is the result of the Wassermann reactions from February, 1919 to October, 1921. From February, 1919 to March, 1921 a total of thirty injections of neo-arsphenamin

were administered in series, the doses ranged from 0.45 to 0.9 gm. at intervals of about two weeks. After the positive reaction was obtained in March treatment with the arsphenamins was purposely stopped and mercury and potassium iodid administered by mouth. It is interesting to note that the heretofore resistive positive Wassermann reaction became negative relatively soon after the cessation of arsphenamin treatment.

<i>Kolmer method.</i>				<i>Old method.</i>	
February, 1919:				Antigen No. 1	4+
				Antigen No. 2	4+
				Antigen No. 3	4+
May, 1920:				Antigen No. 1	3+
				Antigen No. 2	2+
				Antigen No. 3	3+
March, 1921:	0.1	c.c.	4+	Antigen No. 1	3
	0.02	c.c.	4+	Antigen No. 2	1
	0.004	c.c.	—	Antigen No. 3	1
	0.002	c.c.	—		
	0.001	c.c.	—		
August, 1921:	0.1	c.c.	2+	Antigen No. 1	+
	0.02	c.c.	—	Antigen No. 2	—
	0.004	c.c.	—	Antigen No. 3	—
	0.002	c.c.	—		
	0.001	c.c.	—		
October, 1921:	0.1	c.c.	—	Antigen No. 1	—
	0.02	c.c.	—	Antigen No. 2	—
	0.004	c.c.	—	Antigen No. 3	—
	0.002	c.c.	—		
	0.001	c.c.	—		

Comment.—The old method gave reliable and consistent results in this case, but the greater sensitiveness of the new test is shown by comparison of the two reactions.

Case 22.—C. S. H. Male, aged thirty-five.

Denies history and previous treatment. No complaint.

Wassermann reaction taken in the course of a general physical examination by a Health Institute, the reaction was 4+. The patient is free of any demonstrable syphilitic cardiovascular or neurologic involvement.

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 2+	Antigen No. 3 4+
0.002 c.c. —	
0.001 c.c. —	

After twenty-five injections of neo-arsphenamin and fifteen injections of mercury the reaction was as follows:

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 4+	Antigen No. 1 4+
0.02 c.c. 4+	Antigen No. 2 4+
0.004 c.c. 4+	Antigen No. 3 4+
0.002 c.c. 4+	
0.001 c.c. 4+	

Comment.—The very strongly positive reaction after a large amount of treatment suggests a Wassermann-fast condition.

COMPARISON OF THE TWO METHODS OF WASSERMANN REACTION IN TREATED SYPHILITICS

Case 23.—G. W. C. Male, aged forty-eight years.

Infected twenty-two years ago. Three years ago the patient complained of general lack of vigor and easily induced fatigue. The Wassermann test at this time was 4+; many similar reactions have since been obtained. The pupils were irregular and reacted sluggishly to light, the pupillary reflexes were exaggerated. Treatment consisted of arsphenamin, mercury, and K. I. administered at intervals ever since.

	<i>Kolmer method.</i>	<i>Old method.</i>
October, 1919:		Antigen No. 1 2+
		Antigen No. 2 2+
		Antigen No. 3 2+
February, 1921:	0.1 c.c. 4+	Antigen No. 1 —
	0.02 c.c. 3+	Antigen No. 2 —
	0.004 c.c. —	Antigen No. 3 —
	0.002 c.c. —	
	0.001 c.c. —	

Comment.—It is here observed that the test in February, 1921 gives a negative reaction by the old method, but a moderate

positive with the Kolmer technic. There is strong reason to believe that the negative was a false negative.

Case 24.—W. B. Male, aged fifty-five years.

In 1910 had a leukokeratosis and carcinoma of tongue which was successfully treated by electrodesiccation. The Wassermann test at this time was 4+. Treatment consisted of arsphenamin, mercury, and K. I. at intervals ever since.

Recent Wassermann tests are as follows:

	<i>Kolmer method.</i>	<i>Old method.</i>
June, 1920:		Antigen No. 1 2+
		Antigen No. 2 1+
		Antigen No. 3 1+
January, 1921:	0.1 c.c. 4+	Antigen No. 1 1
	0.02 c.c. 4+	Antigen No. 2 —
	0.001 c.c. —	Antigen No. 3 —
	0.002 c.c. —	
	0.001 c.c. —	Antigen No. 1 ≠
		Antigen No. 2 —
		Antigen No. 3 —

Case 25.—B. W. Male, aged forty-eight years.

Infected twenty years ago. About ten years ago had a diffuse syphilitic glossitis. Wassermann reaction at this time was 4+ and many similar reactions since. Treatment consisted of arsphenamin, mercury, and K. I. administered at intervals for many years.

At present the patient has a lingual leukoplakia. The Wassermann reaction is as follows:

	<i>Kolmer method.</i>	<i>Old method.</i>
March, 1920:		Antigen No. 1 4+
		Antigen No. 2 3+
		Antigen No. 3 4+
July, 1921:	0.1 c.c. 4+	Antigen No. 1 —
	0.02 c.c. 1+	Antigen No. 2 —
	0.004 c.c. —	Antigen No. 3 —
	0.002 c.c. —	
	0.001 c.c. —	

Case 26.—J. C. C. Male, aged thirty-six years.

A neurosyphilitic who has been under observation and treatment during the past five years. When first seen he presented

subjective and objective symptoms of cerebrospinal syphilis. The blood Wassermann was 4+ and the spinal fluid was positive in all phases. Treatment consisted of intravenous and intraspinal administration of neo-arsphenamin. The spinal fluid is now negative.

The following blood Wassermann tests are given in order to compare the two methods:

	<i>Kolmer method.</i>	<i>Old method.</i>
July, 1919:		Antigen No. 1 4+
		Antigen No. 2 4+
		Antigen No. 3 4+
November, 1919:		Antigen No. 1 4+
		Antigen No. 2 4+
		Antigen No. 3 4+
January, 1920:		Antigen No. 1 3+
		Antigen No. 2 1+
		Antigen No. 3 1+
March, 1920:		Antigen No. 1 4+
		Antigen No. 2 4+
		Antigen No. 3 4+
August, 1920:	0.1 c.c. 3+	Antigen No. 1 —
	0.02 c.c. 2+	Antigen No. 2 —
	0.004 c.c. —	Antigen No. 3 —
March, 1921:	0.1 c.c. 4+	Antigen No. 1 —
	0.02 c.c. 1+	Antigen No. 2 —
	0.004 c.c. —	Antigen No. 3 —
July, 1921:	0.1 c.c. —	Antigen No. 1 —
	0.02 c.c. —	Antigen No. 2 —
	0.004 c.c. —	Antigen No. 3 —

Comment.—It is seen that in August, 1920 and March, 1921 the old test was negative, but the Kolmer method was still moderately positive. Under further treatment a negative was obtained by both tests.

Case 27.—B. B. Male, aged forty-three.

Infected twenty years ago. Cardiovascular examination negative. The pupils are definitely irregular and react sluggishly to light. No other neurologic abnormalities. Spinal fluid examination is negative. The patient received a total of

seventy-five injections of neo-arsphenamin. For some time prior to receiving this number of injections the Wassermann with the old method was weakly positive and at times negative, whereas the reaction with the Kolmer technic was 4+ with 0.1 c.c. During the continuation of treatment this reaction was changed to 2+ in 0.1 c.c., then 1+, and finally became negative. Finally the reaction with both methods remained negative.

RECURRENT WASSERMANN REACTION

Case 28.—H. Aged twenty-one.

When first seen two years ago the patient had diffuse oral mucous patches. At this time the Wassermann reaction with the old method was 4+ with all antigens. About eight months prior had a chancre followed by a secondary eruption; treatment consisted of intramuscular injections of mercury salicylate.

After five intravenous injections of neo-arsphenamin were administered at weekly intervals the reaction, performed with the old method December, 1919, was:

<i>Old method.</i>	
Antigen No. 1	—
Antigen No. 2	—
Antigen No. 3	—

Subsequently the patient neglected the treatment advised. He, however, received two injections of neo-arsphenamin and protiodid by mouth irregularly.

October, 1920 the reaction was:

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. —	Antigen No. 1 —
0.02 c.c. —	Antigen No. 2 —
0.004 c.c. —	Antigen No. 3 —

Treatment was entirely neglected, and in March, 1921 the reaction was:

<i>Kolmer method.</i>	<i>Old method.</i>
0.1 c.c. 2+	Antigen No. 1 —
0.02 c.c. 1+	Antigen No. 2 —
0.004 c.c. —	Antigen No. 3 —
0.002 c.c. —	
0.001 c.c. —	

Comment.—The history of this case is of interest in demonstrating the value of the new technic in disclosing a relapsing positive Wassermann at a time when the old technic fails to do so. From the point of view of treatment the evidence given is of great importance to the patient.

GENERAL COMMENTS

But a few illustrative cases have been cited; their number could be greatly extended by us, but to no effective purpose. A comparison of the two tests in a large number of cases has convinced us that the Kolmer technic is more sensitive and more elastic, in that it more readily portrays variations in the degree of complement fixation.

The Kolmer technic is going to give us fewer negative reactions than heretofore, and they will not appear as early after the institution of treatment as we have been accustomed to see them. But all observing clinicians have suspected that many of our negative reactions were unreliable and did not represent an extinction of the infection. Many physicians and patients were beguiled into a feeling of illusory security by reason of such negative reactions, and some practitioners were, indeed, completely deceived by them, to their patient's detriment. Kolmer's method should accomplish incalculable good by restraining physicians from a too early suspension of therapeutic measures. Clinical experience is in complete accord with the findings of the newer test, inasmuch as serologic relapses and likewise recurrence of symptoms have not been uncommon in the type of cases under discussion.

The question might be asked, Is the Kolmer method not unduly sensitive? We can only reply that we have not thus far had any positive reactions in non-syphilitics, and we have strong reason to believe that in syphilitics under treatment, where the Kolmer method was positive and the older Wassermann technic negative, that the fault lay with the latter. As a matter of fact, we believe that the Kolmer technic is not sufficiently sensitive to detect the reagin in all cases of syphilis, and we believe that some negatives with the Kolmer method do

not represent definitive cures. But we regard the new method as a distinct and important advance over those previously in use. It represents at least as great an improvement as the introduction of the cholesterolized antigens some years ago, and we believe, indeed, that it marks a more important progress.

CONCLUSIONS

We have employed the Kolmer modification of the Wassermann test in about 2000 instances, and have compared the same with the older three-antigen technic. As a result of this study we would formulate the following opinions:

1. The Kolmer method yields distinctly more sensitive results than the older method, being frequently positive when the latter is negative.

2. It does not appear to give false positives in non-syphilitic subjects, nor in patients who have been treated for syphilis.

3. It appears to give an earlier positive in primary syphilis, the value of which will be readily appreciated.

4. It is much slower than the older method to become negative under treatment, because it is more delicate in detecting minute amounts of reagin in the blood.

5. By reason of this it insures to patients more adequate and protracted treatment.

6. It harmonizes with the clinical findings better than the older method which was notorious for many unwarrantable negative reactions.

7. Its quantitative character permits one to better gage the effect of antisyphilitic treatment. It likewise gives suggestive evidence in connection with the so-called "Wassermann-fast" cases.

8. We regard the Kolmer modification of the Wassermann test as a most important advance, and one calculated to shed added light on the detection of obscure syphilis and in the ultimate determination of the effects of treatment.

CONTRIBUTION BY DR. JOHN A. KOLMER

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AN ANALYSIS OF SOURCES OF ERROR IN THE WAS- SERMANN REACTION WITH THE REQUIREMENTS AND PROPERTIES OF A NEW METHOD

IN their attitude toward the Wassermann test physicians may be divided into those who have considerable confidence in the reliability of the test and especially in the significance of the positive reaction both in the diagnosis of syphilis and as a guide to therapy, those who have little or no faith in the test in either a positive or negative way, and those who have found it generally satisfactory providing weakly positive reactions are disregarded. Therefore there is probably no other laboratory test the subject of as much disagreement between clinician and laboratorian; this is to be particularly regretted because no other strictly laboratory test possesses an equal importance or greater possibilities for good as a diagnostic means of a disease which is everywhere on earth among all classes of human beings, irrespective of sex and age. The disagreement is based upon difficulties and errors on the part of both clinician and laboratorian; I shall attempt to analyze these, offer logical explanations for both sides, and briefly summarize my efforts toward their solution and correction.

BIOLOGIC SOURCES OF ERROR AFFECTING THE INTERPRETA- TION OF THE WASSERMANN REACTION

There are certain fundamental or inherent sources of error affecting the interpretation of the Wassermann reaction from

the viewpoint of both clinician and laboratorian, a correct understanding of which will go far toward improving its status.

The reaction is not biologically specific for syphilis because the antigen is not specific and the test is not a true antigen-antibody reaction in the original sense of Bordet and Gengou. In syphilis the *Treponema pallidum* brings about in the blood or spinal fluid, or both, the presence of a peculiar substance which under favorable circumstances fixes complement in the test-tube in the presence of lipoids contained in the tissue extract erroneously designated as the antigen. This substance is probably not a true antisyphilitic antibody, and its presence or absence in the blood does not appear to bear any constant relation to the stage of the disease because in latent syphilis when the treponemata have been forced into a relatively inactive state and when, accordingly, the largest amounts of antibody should be found, this substance may be present in such small amounts as to escape detection. On the other hand, it bears a closer relation to the severity or activity of the disease and is apt to be found in largest amounts when active lesions and symptoms are present. Neisser has called this substance "reagin"; it is characterized by its lipodotropic activity or ability to fix complement with suitable lipoids, and its presence in the body fluids in disease is an index of infection rather than immunity.

Furthermore, the lipoids contained in the so-called antigen are not specific, that is, the extract used as antigen may be, and usually is, prepared of normal non-syphilitic tissues. While Wassermann and Detre originally believed that these extracts owed their virtues to the presence of products of pallida, it is now conclusively proved that this is not the case. Biologically true antigens of pure cultures of pallida are now known to be almost useless for the Wassermann test, and it is, indeed, fortunate for medical science that neither of these pioneer investigators had pure cultures at his disposal in 1905; both were compelled to use tissues containing pallida, and both unwittingly secured extracts containing sufficient lipoids to make them worth while and the results worth reporting. Both would have done

equally well by extracting normal tissues, but no one dreamed of this possibility until a few years later. Granting that the Wassermann test as ordinarily practised is not specific because the antigen is non-specific, the question naturally arises:

Is the Reagin or Wassermann Antibody Found Only in Syphilis?—If this substance is found only in syphilis why give the nature of the reaction more than a passing comment? Any one who will take the trouble of reviewing the literature on the Wassermann reaction can hardly escape the impression that this reagin may be found in almost every disease to which human flesh is heir, because some one at some time is almost sure to have reported positive reactions in a large number of diseases other than syphilis. Unquestionably a similar reagin is to be found in *frambesia tropica* or yaws, but further than this positive statements are not fully justified by the available facts based upon work conducted during the past five years. Leprosy, and especially the nodular type, is commonly regarded as a disease in which the Wassermann test may be positive, but the possibility of the coexistence of syphilis in those lepers who have yielded positive reactions has not always been ruled out. Scarlet fever is another disease in which many investigators have reported positive reactions, although it is now quite definitely proved that this is not the case unless syphilis is also present. Positive reactions have been reported in malaria, diabetes mellitus, late pregnancy, during febrile states, and especially in pneumonia, tuberculosis, and typhoid fever, in nephritis with uremia, and other conditions.

It is granted that these diseases may bring about such profound chemical changes in the blood as to exert an anticomplementary influence and therefore yield a falsely positive reaction, but there is lacking a uniformity of opinion among both clinicians and laboratorians on the question of true positive Wassermann reactions in these diseases, and latent syphilis may be present in some cases at least and be the true explanation for from 2 to 10 per cent. of the reported reactions.

Personally I am quite sure that the reagin occurs in *frambesia tropica* because of the uniform evidence to be found in literature

plus the opportunity of making serologic studies upon a case diagnosed and thoroughly studied by my colleagues, Dr. Schamberg and Dr. Klauder¹; I am doubtful about leprosy, and have not, to the best of my knowledge, found positive reactions in non-syphilitic persons with the other conditions mentioned above. Frambesia is caused by a spirochete very closely related to pallida, and the production of the reagin is to be expected; for the same reason I am prepared to believe that a similar reagin may be produced in other spirochetic infections, as infectious jaundice and possibly in some spirillar infections, as chronic Vincent's angina and spirochetic gingivitis, although systematic studies do not appear to have been made in these diseases. Therefore, while not biologically specific because the antigens ordinarily employed are non-specific, the

Wassermann reaction is practically specific for syphilis in those localities where frambesia tropica does not occur, because the peculiar lipodotropic reagin responsible for the reaction is known definitely to occur in only these two spirochetic infections; leprosy may be included, but further investigations will probably show that the serum and spinal fluid in this disease in non-syphilitic individuals do not give positive reactions.

I believe that falsely positive reactions with the sera of healthy non-syphilitic individuals or of non-syphilitics during the febrile stages of scarlet fever, pneumonia, typhoid fever, tuberculosis, and malaria, in diabetes, psoriasis, pregnancy, etc., are due to technical errors, and especially in the kind and amount of antigen employed with particular reference to the amount of cholesterin; this by no means denies the possibility of falsely positive reactions occurring in these conditions, but when they are observed I believe that they are explainable on the basis of technical error in the conduct of the test.

Occasionally when the Wassermann test is conducted as a matter of routine the clinician is greatly surprised by a totally unexpected positive reaction and the laboratory is called upon for an explanation. Not infrequently this discrepancy is due to a biologic error, but this time on the part of the clinician, because

Syphilis may escape clinical detection, but yield positive Wassermann reactions. Cases of prenatal and acquired syphilis insufficiently treated or not at all, but in the latent stages, with indefinite lesions and symptoms, or practically none, may occur in the practice of every physician irrespective of his special field of work, and yield true positive Wassermann reactions. It is now so well known that syphilis may manifest itself in so many different ways that it is to be regretted that the knowledge of this disease possessed by not a few practitioners is confined to the primary sore, secondary eruptions, and the skeletal gumma without an adequate appreciation of the great many different lesions of various internal organs and systems which may be produced by syphilis in its tertiary stage. As Osler is so frequently quoted: "Know syphilis in all its manifestations and relations and all other things clinical will be added unto you." I am mentioning this phase of the problem at the present time in order to advise the clinician against lightly brushing aside the unexpected or weakly positive reaction reported by a good laboratory regardless of the sex or respectability of his patient; these results are not always due to technical errors in the laboratory and not infrequently indicate the presence of syphilis.

I feel perfectly safe in predicting that *as clinical and pathologic knowledge of syphilis is developed the more emphasis will be placed upon the significance of weakly positive reactions. Furthermore, in the present state of our highly perfected Wassermann technic every laboratory conducting the test should have enough faith in its results to place some significance and confidence in its weakly positive reactions.*

Another source of error on the part of the clinician well worth remembering is that *a positive Wassermann reaction does not necessarily indicate that a particular lesion is syphilitic*; for example, a tuberculous ulcer may occur in the larynx of an individual with latent syphilis. Treatment has no influence upon the ulcer, and as a result the laboratory is wrongly blamed for error and misleading reports. Patients are even more likely than physicians to interpret every ache, pain, and lesion as syphilitic, once this disease is suspected or known to be present.

So far our discussion has been confined to the positive Wassermann reaction; it is almost equally important to bear in mind that

The Wassermann test may biologically yield falsely negative reactions because the disease may be so latent that there is insufficient reagin produced to afford detection. Of course, this varies a great deal with the technic employed in the laboratory, to which special attention will be given later. As my colleague, Dr. Schamberg, has repeatedly stated, "the Wassermann test is not too delicate, but rather is not delicate enough."

Warthin has shown that pallida may exist in the tissues with practically no inflammatory reaction and has demonstrated their presence after death in individuals who gave negative Wassermann reactions during life. These facts render imperative continued efforts on the part of the immunologist to render the Wassermann test as sensitive as is possible with practical specificity, but even when this is accomplished *there is likely to be a limit to the diagnostic sensitiveness of the reaction, because if there is practically no reagin in the blood or spinal fluid, or both, it is obvious that true positive complement-fixation reactions cannot take place in the test-tube.* For this reason too much significance cannot be placed on a single negative blood Wassermann reaction if there are any grounds whatsoever for suspecting syphilis; this is especially true if the laboratory itself is one that has little or no faith in its weakly positive reactions. Furthermore, *it renders imperative the use of as sensitive a test as is possible with practical specificity* for diagnosis, and whenever the reaction is employed as a guide in treatment in order to avoid the regrettable error of undertreating the disease. In connection with this subject of biologically falsely negative Wassermann reactions is it worthy of remembrance that while the blood may yield a negative reaction, the spinal fluid may react positively, and some investigators have found that acute alcoholism, ether, and chloroform anesthesia may dissipate syphilis reagin in the blood and result in a temporary falsely negative reaction with the serum of a syphilitic.

With this discussion of certain biologic factors which may

affect the Wassermann reaction in both a positive and negative way on the sides of both clinician and laboratorian, we may now proceed to a discussion of certain technical sources of error which largely concern the laboratorian.

TECHNICAL SOURCES OF ERROR AFFECTING THE INTERPRETATION OF THE WASSERMANN REACTION

This is obviously too large a subject to discuss in detail. Everyone acquainted with the primary principles of complement fixation must realize the numerous sources of error in the conduct of the Wassermann test, and especially as concerns the extract employed for antigen and the hemolytic system.

Wassermann's test has undergone so many modifications that the phrase "Wassermann test" has become only a synonym for complement fixation in syphilis²; these modifications have been developed to either shorten the method, render it more simple and economical, or to increase its sensitiveness and practical specificity. The test is simple if everything is properly prepared and working smoothly, but because of a large demand it is inevitable that many attempt its performance with insufficient experience to cope with its difficulties and numerous sources of technical error. But

Too much emphasis should not be placed upon the possibility of technical errors. because great advances have been made in our knowledge and experience with complement-fixation technic, and doubtless the majority of serologists bring to bear upon their work a commendable degree of skill, experience, and attention to details. In other words, the sources of biologic error previously discussed and affecting both clinician and laboratorian alike are not to be overlooked, and the whole burden hastily and unjustly thrown upon the shoulders of the technician. Of all sources of technical error, probably

The Kind and Dosage of Antigen is Most Important.—Regardless of the care with which the test is done, a defective antigen or a good antigen in defective dosage cannot yield uniformly satisfactory reactions. Cholesterolized antigens are known to be the most sensitive, but may yield falsely positive

reactions with normal sera or the sera of individuals with diseases other than syphilis and frambesia unless properly titrated and employed with a properly adjusted hemolytic system, under which conditions I believe they are perfectly safe.

In addition to the antigen, the kind of hemolytic system and kind of primary incubation employed have important influences upon complement fixation in syphilis and other infections. The antihuman hemolytic system, for example, is believed to be more delicate than the antisheep, and this is true insofar as the anti-sheep system in the original Wassermann test is concerned, but when the antisheep system is more properly and delicately adjusted it possesses equal and even superior sensitiveness, because workable with a smaller amount of complement which increases the sensitiveness of the complement-fixation reaction.

Furthermore, agglutinins are commonly encountered in the antihuman system in both the hemolysin and human sera, and these are likely to render the readings difficult and foster the spirit and practice of disregarding weakly positive reactions. With sufficiently powerful hemolysin the antihuman system is perfectly satisfactory, but in many laboratories the hemolysin is weak because relatively so difficult of preparation, in which case these criticisms of the antihuman system are warranted.

With numerous technical details of this kind able to modify the results, not to mention the question of individual accuracy and care on the part of the technician,

It is not surprising that different laboratories may report varying results with portions of the serum of the same person, or that widely varying results may be reported from the same laboratory on tests conducted with the blood of the same individual at close intervals. This is particularly true with the sera of individuals yielding weakly positive reactions when slight differences in technic, and especially in the antigens, may throw the reaction either toward the negative or positive. Too much emphasis must not be placed upon these results when estimating the true value of the complement-fixation test in syphilis because they are due to technical errors susceptible of correction rather than to fundamental or biologic errors over which the labora-

torian may have no command. Rather, these results should teach the clinician that a Wassermann test may vary in its results according by whom it is done; that the laboratory or immunologist should be selected with as much care as a consultant in other specialities would be, and finally, that it is highly desirable to have a standardized technic of superlative reliability.

ADVANTAGES OF STANDARDIZATION OF THE WASSERMANN REACTION

It is not difficult to understand that certain advantages would follow the general adoption of a standardized test of proved and superior merit. In the first place, it would tend to increase the confidence of the medical profession in the test as a means of diagnosis of syphilis. At the present time, when there is a wide-spread movement for improving methods for the control and treatment of syphilis, a thoroughly reliable serum test cannot fail to be of great value.

Furthermore, a standardized test would enable the profession to reach quicker and more reliable conclusions regarding the merits of different methods of treatment. If treatment is to be guided by serologic reactions it is imperative that the tests be conducted with a fairly uniform technic, as otherwise a comparison of serologic results is misleading and almost worthless. In my opinion the Wassermann reaction as ordinarily conducted is frequently lacking in sufficient sensitiveness, and that, as a result, the disease is insufficiently treated. This is an additional and important reason for increasing the specific sensitiveness of the complement-fixation test for syphilis, and an acceptable standardized test must fulfil this essential requirement.

The only possible disadvantage of adoption of a standardized test is the stifling of further investigation. I cannot conceive of this being a result; in our present ignorance of the mechanism of the reaction it is not possible to develop a test aspiring to be perfect and the last word on the subject. Rather, I expect that standardization will stimulate investigation and gradually lead to the evolution of a superior technic.

The Author's Conception of Standardization.—*In my opinion standardization of the Wassermann reaction has not meant the adoption of any of the present methods or efforts toward evolving a technic simply to yield uniform results in different laboratories, but a thorough investigation into every technical phase of the test and a comparative study of all the better known methods for the purpose of determining and selecting the best for incorporation into a new technic.* Possibly the easiest way for standardization to meet the sole requirement of uniformity would be the adoption of the original Wassermann test with a few modifications, but such a plan could not be expected to succeed because the test would be lacking in sufficient sensitiveness. In other words, standardization first means the building up of a technic possessing the greatest possible degree of sensitiveness consistent with practical specificity; I have worked with the idea that the complement-fixation test for syphilis as ordinarily conducted is not too sensitive, but not sensitive enough, of course bearing in mind that non-specific positive reactions are worse than falsely negative ones, and to be carefully avoided.

The Author's Investigations on Standardization of the Wassermann Test.—It was with this idea in mind of carefully studying all technical phases of the complement-fixation reaction and of different modifications of the Wassermann test for syphilis that a series of investigations were started six years ago which have continued up to the present with interruptions due to war time activities.³ I realized that the task was big before a start was made, but did not conceive that it would require the very large amount of work that has been done. As our investigations proceeded it became evident that every detail, regardless of how trivial it may at first appear, was worthy of careful study. My associates and myself have striven always to conduct the work without preconceived ideas and without bias. Experiments were commonly repeated a sufficient number of times to enable us to draw conclusions. It can scarcely be hoped or expected that we have escaped technical errors and erroneous conclusions, but we have faithfully described what we have done and what we have observed.

These investigations have finally enabled me to build up a new complement-fixation test for syphilis which I hope will receive a sympathetic reception on the part of serologists and clinicians, and that they will at least consent to give it a fair trial alongside of their own technic. I have not called it a standardized test because it must earn that designation by common consent. But experience with the test has been most favorable, and I am hoping that it may, at least, prove a starting-point toward the adoption of a standardized technic. A new antigen and many technical improvements are included; also a method for establishing a standard unit of antigen by a central laboratory, as the hygienic laboratory has established standards for measuring the strength of antitoxic sera.

My aim has been to develop a technic possessing six requirements, as follows:

1. As high degree of sensitiveness as is permissible with specificity.
2. Practical specificity.
3. Technical accuracy and uniformity in results.
4. Yield a quantitative reaction.
5. Simplicity of technic.
6. Economy.

The new complement-fixation test for syphilis has aimed to meet these requirements as follows, a fuller discussion and all technical details being given elsewhere*:

- I. *The requirement of sensitiveness* by the following procedures:
 - (a) By using a highly sensitive antigen.
 - (b) By using relatively large amounts of antigen.
 - (c) By using relatively large amounts of serum and spinal fluid.
 - (d) By heating sera for only fifteen minutes at 55° C. instead of for thirty minutes.
 - (e) By using a mixture of guinea-pig complements prepared in a manner tending to increase sensitiveness to fixation.
 - (f) By mixing serum and antigen for a brief period before the addition of complement.

- (g) By using a primary incubation of fifteen to eighteen hours in a refrigerator at 6° to 8° C. plus ten minutes in a water-bath.
- (h) By close adjustment of the hemolytic system.
- (i) By using an antisheep or antiox hemolytic system, although the test can be conducted with an anti-human system.
- (j) By reading the reactions within three hours after the conclusion of the secondary incubation.

II. *The requirement of practical specificity by:*

- (a) Close adjustment of the hemolytic system to a primary incubation of fifteen to eighteen hours at 6° to 8° C.
- (b) Careful titration of antigen under conditions rendering the dose employed suitable for this kind of primary incubation.
- (c) Including numerous and adequate controls.

III. *The requirement of technical accuracy and uniformity in results by:*

- (a) Adopting the principle that pipeting relatively large amounts of fluid (0.2 to 1 c.c.) tends to greater accuracy than measuring smaller amounts (less than 0.2 c.c.).
- (b) Using a total volume of 3 c.c. with sufficient corpuscles and test-tubes of suitable size to yield clear, sharp, and easily read reactions.
- (c) By using a reading scale prepared each time the tests are conducted and with the same reagents.

IV. *The requirement of a true quantitative reaction*, so important in connection with the use of the complement-fixation test as a guide and control in treatment, has been met by working out a series of five dilutions of patient's serum and spinal fluid which may be set up rapidly and accurately.

V. *The requirement of simplicity* has been met insofar as experienced serologists are concerned. Simplicity is but a relative term, inasmuch as the simplest technic is a com-

plicated problem for the inexperienced and insufficiently-trained worker, whereas a more complicated technic is perfectly simple to the experienced serologist. I am quite sure that my new test can be satisfactorily conducted by any person possessing a working knowledge of the technic of complement fixation.

- VI. *The requirement of economy* has been met insofar as materials are concerned; in regard to time the new test is not a short-cut method and is not shorter than other methods in general use.

In conclusion, a few lines may be added on the subject of uniformity in results. It must be emphasized that the anti-complementary activity of serum or spinal fluid is very important in relation to reactions, and for this reason tests conducted with portions of the same specimen of blood in different cities cannot be expected to yield absolutely similar results, nor even in the same city, if serologists vary in their methods of preserving blood until the tests are conducted.

Two or more serologists working in the same or different laboratories testing portions of a sample of blood or spinal fluid from one person should agree at least upon the question of positive or negative reactions; in my experience most variation occurs with sera yielding weakly positive or borderline reactions. Slight discrepancies in the reports on the degree of complement fixation must be expected, inasmuch as the personal equation plays an important part in reading the degree of hemolysis, as it does in matching colors in other lines of work. Slight discrepancies of this kind do no harm as long as the primary and fundamental question of whether a serum does or does not yield a positive or negative reaction is untouched, and particularly with sera yielding borderline results.

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FACTORS OF PROGNOSTIC SIGNIFICANCE IN PERSISTENT HIGH BLOOD-PRESSURE

IN the course of our studies we have observed a number of patients that exhibited persistently high blood-pressure as an obtrusive symptom. Heretofore we have discussed this condition chiefly from the standpoint of diagnosis and management. We have also dwelt upon the importance of differentiating these cases with hypertension according to the various causes that are responsible for persistent elevation of arterial pressure. Now let us consider the subject of high blood-pressure from a somewhat different viewpoint and inquire into the prognostic value of certain factors in those who show this circulatory disturbance. Such a discussion is distinctly of practical value, for, as Sir James Mackenzie has emphasized, there is no phase of medicine of equal importance that is so difficult to master and yet is so generally neglected as the subject of prognosis. This is especially true in connection with patients who have a persistently high blood-pressure, because in dealing with them, along with other difficult problems, questions invariably arise as to what will be their ultimate fate, and what effect, if any, will the high-pressure have on the duration of life.

To formulate an intelligent opinion about the prognosis of any chronic condition it is essential not only to observe a number of cases but also to have such cases under observation for a considerable period of time. Therefore, in order to present to you some data bearing upon the prognosis of vascular hypertension, a group of 160 cases has been collected. These cases

have all exhibited a persistently high blood-pressure, that is, in every instance the average systolic pressure has been 170 millimeters of mercury or over, and they have all been under observation from two to ten or more years. During the time that the patients in this group have been under observation all have been frequently examined; repeated blood-pressure readings have been made; and the urine has been studied on different occasions. As you have already learned, cases of persistently high blood-pressure are more often encountered in private than in hospital practice. Therefore the majority of the cases comprising this series belong to the former group. This material has been studied with a view to determining what the duration of life has been after the high pressure was recognized, if death occurred, what has actually been its cause, and whether the ultimate prognosis bore any discoverable relationship to the height of the pressure or to its etiology.

As has been frequently pointed out, vascular hypertension cannot be regarded as a disease, but must be looked upon rather as a symptom of some underlying cause. Since the conditions capable of producing high blood-pressure are varied, it is necessary first of all to study this group of cases from the standpoint of the etiology of their increased vascular tension. From our previous discussions of this subject you must realize how difficult it is in some cases to satisfactorily determine the underlying cause of a high blood-pressure. This difficulty is heightened by the fact that when vascular hypertension has existed for any length of time secondary changes invariably take place in the heart, kidneys, and blood-vessels. Therefore in advanced cases it is often well-nigh impossible to determine definitely the primary cause of the hypertension; whether renal or vascular changes are the underlying factor. Furthermore, in any individual several possible etiologic factors may be present at one time. With these difficulties clearly in mind, it is evident that differences of opinion are likely to occur whenever an effort is made to subdivide a series of high blood-pressure cases according to their etiology.

From a study of the clinical and laboratory records of these

cases which are under consideration it is apparent that they can be divided into three main groups: (1) Those in whom the high blood-pressure is the result of some type of chronic nephritis; (2) those in whom vascular changes are primarily responsible for the elevation in pressure, and (3) those in whom a high systolic pressure is incident to a primary cardiac condition, such as aortic insufficiency.

The second group, those in whom vascular changes are responsible for the hypertension, is susceptible of further etiologic subdivision. In the majority of this group the high pressure may be looked upon as an expression of some phase of arteriosclerosis. In a considerable number of these, toxemias or chronic infections furnish the basis for the arteriosclerotic changes, but a larger proportion of them fall under the head of primary, essential, or idiopathic hypertension, the hyperpiesis of Sir Clifford Allbutt. In this connection it should be recalled that there is a school of clinicians who maintain that arteriosclerosis never causes a high blood-pressure, but, on the contrary, that vascular spasm and the associated hypertension are the primary conditions which are responsible for the subsequent degenerative arterial changes. However this may be, and there is no doubt but that in not a few instances high blood-pressure precedes demonstrable degenerative renal changes, it is not our province to enter here into a discussion of this much disputed point. For the purpose of this study it seems justifiable to apply the term "arteriosclerosis" to a large proportion of the cases in this group in whom hypertension is either the cause of or is associated with definite arterial degeneration. In others again the rise in blood-pressure has been coincident with the menopause. They represent a type of hyperpiesis that has been termed "climacteric hypertension." There is a third group in whom the vascular spasm, which has been responsible for the elevated pressure, is apparently due to some endocrine disturbance. In some of these there is obvious evidence of hyperthyroidism; in a few others the clinical phenomena suggest the existence of some dysfunction of the pituitary, and possibly of the adrenals.

A word may be said as to the criteria used in dividing these cases in accordance with this grouping. Renal disease was regarded as the underlying cause of the hypertension only when from the start there were persistent and definite evidences of kidney involvement. Such involvement was assumed to be present when alterations in the specific gravity and quantity of urine existed (that is, abnormally high or low fixation of specific gravity, oliguria, or polyuria, especially if the latter was nocturnal); when albumin and casts were persistently demonstrable in the urine; and when there were evidences of disturbed renal function, as shown by the phthalein elimination and the blood chemistry.

The diagnoses of essential hypertension or arteriosclerosis were made only in those patients who consistently failed to show any evidence of renal involvement or in whom only slight and inconstant urinary changes were observed after a high blood-pressure had existed for some years. The term "climacteric or menopausal hypertension" has been applied to a certain group of cases that developed a primary hypertension at or about the time of the menopause, but in whom noteworthy renal changes were lacking. Of late years considerable interest has been shown in this group of hypertensive cases. Robert G. Torrey was among the first to emphasize the frequency of high blood-pressure at the time of the menopause, later the subject was more fully discussed by Riesman and by Hopkins, and recently F. Wright and Cummings have both written about this condition.

A small number of patients in whom the hypertension began before the age of forty, who exhibited no evidence of syphilis or of renal or endocardial disturbance, but who showed clearly symptoms pointing to dysfunction of the thyroid, pituitary, or some combination of these or other glands of internal secretion, have been regarded as instances in which the vascular spasm had as its basis some endocrine disturbance. It must be admitted that while the assumption seems justified that cases of this nature occur, our present knowledge of perverted internal secretions is so meager that they are but little understood.

A high systolic pressure is one of the vascular phenomena frequently associated with aortic insufficiency. In this series there are a few cases in whom the existence of a high systolic pressure could only be attributed to the presence of a definite, chronic regurgitant lesion of the aortic valve, the outcome of a preceding infective endocarditis and not the result of lues.

In this group of 160 cases the persistent high pressure has been regarded as due to some form of chronic nephritis in 81; to a primary vascular cause in 74, and to be the result of aortic regurgitation in 5. The number of nephritic and vascular cases, therefore, is almost equal. These cases of vascular origin may again be subdivided as follows: 52 are instances of hyperpiesis or arteriosclerosis; 16 are examples of climacteric hypertension, and 6 may be looked upon as the result of some endocrine disturbance.

Such relationship as sex and the diagnoses bear to each other may be seen in the following table:

	Males.	Females.
Chronic nephritis.....	45	36
Hyperpiesis and arteriosclerosis.....	22 } 26	30 } 48
Climacteric hypertension.....	0 }	16 }
Endocrine disturbances.....	4 }	2 }
Aortic insufficiency.....	2	3
	<hr/> 73	<hr/> 87

This table indicates that in the men hypertension was due to some form of nephritis almost twice as often as it was due to any vascular cause, whereas in the women vascular disturbances decidedly exceeded renal lesions as an etiologic factor. From a consideration of the whole series it is apparent that in men nephritis was the cause of hypertension somewhat more often than in women, but that high blood-pressure of purely vascular origin was almost twice as common in women as in men. This discrepancy is largely the result of the menopausal origin of many cases of primary hypertension in women.

Up to the present time 60 patients of this series have died, or over one-third of the total number. Of this 60 who have died, 45, or 75 per cent., suffered from some type of chronic

nephritis; 13, or 21.7 per cent., were arteriosclerotics; 1 was an endocrine case, and 1 had aortic insufficiency.

Of the 100 cases that are still alive, 36 are chronic nephritics; 39 are instances of arteriosclerosis; 16 come under the head of menopausal hypertension; 4 are cases of aortic insufficiency, and 5 presumably suffer from some endocrine disturbance.

These figures strongly suggest the important bearing that etiology has upon the prognosis of cases of hypertension. As might be expected, the greatest mortality existed among the chronic nephritics, of whom 55.5 per cent. terminated fatally and about 28 per cent. died within three years. Whereas only 17.6 per cent. of the arteriosclerotics are dead and no cases of menopausal hypertension have thus far succumbed. Of the total number of cases that are dead, death has been three times more frequent in the nephritics than in those suffering from other conditions. The favorable prognosis in menopausal hypertension is a practical point worthy of emphasis.

An inquiry into the exact cause of death in the 60 fatal cases shows that the largest number, 17, or 28.3 per cent., succumbed to chronic cardiac dilatation; 14, or 23.3 per cent., died of cerebral hemorrhage; 11, or 18.3 per cent., died of uremia; and in 6, or 10 per cent., angina pectoris proved the terminal event. Pneumonia and carcinoma were each responsible for 4 deaths. Three succumbed to diabetes and 1 to acute pericarditis. Chronic cardiac failure and cerebral hemorrhage, therefore, proved the commonest causes of death in this group of cases with persistently high blood-pressure.

The causes of death taken in relationship to the various diagnoses show that of the 45 nephritics that died, in 11 death was due to uremia, in 11 it was the result of chronic cardiac dilatation, and 11 died of apoplexy, a striking uniformity in the incidence of these terminations. In 4 nephritics the fatal event was angina pectoris; 3 developed fatal carcinomas; 3 who suffered coincidentally with diabetes mellitus succumbed in diabetic coma; 1 nephritic died of pneumonia and 1 developed a terminal pericarditis. Of the 13 arteriosclerotics that died, 5 succumbed with dilated hearts; 2 from cerebral hemorrhage; 3

developed terminal pneumonias; 2 died of angina pectoris, and 1 of carcinoma. Chronic cardiac failure proved fatal to one endocrine case, and apoplexy to a case of aortic regurgitation.

A study of the ages at which death occurred is of some prognostic interest. Of the 6 cases that were observed between the ages of 25 to 40, 66.6 per cent. are dead. Next to the largest number of cases occurred between the ages of 40 to 60, of these 25 per cent. have succumbed. The largest group fell between the ages of 60 to 80, of which 41.3 per cent. have terminated fatally, and of the small group that was observed after the age of eighty, 75 per cent. are dead. The greatest mortality, therefore, occurred among the oldest and youngest groups in this series. The mortality was high among the younger individuals of the series because of the rapidly progressive types of nephritis from which most of them suffered. The greatest mortality occurred among the aged because in this group terminal infections were common and in them degenerative visceral changes were far advanced. After the age of forty the percentage of deaths increased with each decade of life.

Efforts to draw prognostic conclusions from the height of the blood-pressure alone have proved uncertain and unreliable. Of the 29 cases that exhibited a systolic blood-pressure of 220 or over, 11 died within three years; 1 lived for five years, and 1 for six years. On the other hand, of the 16 that are still alive with this excessively high blood-pressure, all have lived at least two years, and 11 have lived from five to twelve years since they came under observation. In short, more patients of this series are alive today with systolic blood-pressures of 220 or over than have succumbed, and as many are alive after five years as died within three years. Much the same result is obtained when a different group is studied. Seventy-nine of the series exhibited systolic blood-pressures of 200 or over. Of this number, 50 are still alive, and of these, 20 have lived for five years or more. Of the 29 that are dead, 23 died within five years after coming under observation, but 6 lived for five years or over.

No more helpful results are obtained when the diastolic

pressure is taken as the prognostic index. Of the entire series there were 90 cases that had diastolic pressures averaging 110 millimeters of mercury or over. Of this number, 53 are still alive, half of whom have already lived five years or more. Of the 37 that are dead, 26 died within five years after coming under observation, and 11 survived for five years or more. It would seem fairly evident, therefore, that the height of the blood-pressure, *per se*, whether the systolic or the diastolic is considered, bears little or no relationship to prognosis. The important prognostic factor is the underlying cause of the hypertension.

The occurrence of certain complications that are frequently associated with cases of high pressure have also been studied in connection with this series, with the idea of discovering, if possible, whether or not in this way any prognostic conclusions can be drawn. In all cases of hypertension studies of the eye-grounds are of acknowledged importance. In this series there were 30 instances in which marked changes in the eye-grounds were demonstrable, or 18.75 per cent. Twenty-five of the 30 cases with eye-ground changes were definitely nephritic. Of these 30 cases with retinal manifestations, 16, or just over 50 per cent., are dead. Transient paralyses were observed in 10.6 per cent. of cases. These temporary changes in the central nervous system apparently bore no relation to prognosis, since they occurred over twice as frequently in those who are still alive as in those that died. Angina pectoris occurred in 18.3 per cent. of the entire series, of whom only 3.7 per cent. died of angina. One-half of the cases that exhibited angina pectoris were nephritics. A dilated aorta was observed in 15 per cent. of the total series. It was observed with equal frequency in cases of primary hypertension and arteriosclerosis and in cases of nephritis. Out of the entire group of 160 patients with high blood-pressure, there were only 27 that did not show definite evidence of left ventricular hypertrophy upon ordinary physical examination. With the possible exception of eye-ground changes, the above noted complications have apparently no important prognostic significance.

From our study, therefore, of this series of 160 cases with chronic vascular hypertension due to various causes, we may come to certain conclusions that have a bearing on prognosis:

1. Chronic renal disease is chiefly responsible for hypertension in men, whereas in women hypertension is more often the result of some primary vascular disturbance. The frequent occurrence of climacteric hypertension largely accounts for this difference.

2. In cases of persistent hypertension the etiology of the high blood-pressure bears a definite relationship to the prognosis. The mortality is greatest in those cases of hypertension that are due to chronic nephritis. Menopausal hypertension is conspicuously benign.

3. About 28 per cent. of the chronic nephritics that exhibit marked high blood-pressure succumb within three years of the time they come under observation.

4. The chief causes of death in cases of high blood-pressure are cardiac failure and cerebral hemorrhage.

5. After the age of forty the percentage of mortality in patients with hypertension increases with each decade.

6. The height of the blood-pressure, *per se*, whether the systolic or the diastolic pressure is considered, bears no definite relationship to prognosis. The most important factor in determining the prognosis is the underlying cause of the high blood-pressure.

CLINIC OF DR. JOHN H. MUSSER, JR.

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LEUKEMIA

LEUKEMIA is a disease that presents many interesting phases in its clinical manifestations, its blood-picture, the result of treatment, and lastly, in speculations as to its pathogenesis. First described by Virchow in 1845 as a rare disease, leukemia, in spite of our familiarity with its manifestations and the ease with which it can be recognized, still remains a rare disease, that is to say, it is rare, in that we are not likely to meet it frequently in every-day work. In the University Hospital Medical Dispensary, to which are referred frequently unusual diseases or diseases which require particular treatment, we have seen only 3 cases within the past year in a total number of 1823 new cases. The disease, therefore, is, you see, one which is relatively rare. Leukemia occurs in two types: the lymphatic and the myelogenous or myeloid or splenomyelogenous, to use synonyms which have been applied at various times to this disease. These two forms, in turn, may be either acute or chronic. Of these types the chronic myelogenous form is decidedly more frequent than the chronic lymphatic form, but of the acute forms the lymphatic type is the predominating one, although the figures on the frequency of this type are probably not accurate, owing to faulty staining methods employed up until a few years ago. The disease has also been divided into the so-called primary and secondary types. The division suggested would make leukemia analogous to pernicious anemia. The primary type is the ordinary type which we are accustomed to see. Secondary leukemia is a type of disorder in which there is the presence of a large number of lymphocytes in the blood or abnormal cells of the myeloid

type. This division hardly seems justifiable, because the conditions which produce the so-called secondary leukemia are disorders found chiefly in childhood or disorders which are very obviously producing myeloid change in the hemopoietic system and which are more or less transitory.

The acute types of leukemia are decidedly more frequent in early life, decreasing very rapidly in relation to the chronic forms, so that in the later years of life the chronic types of leukemia are the predominating ones. Chronic leukemia is rare before the twentieth year of age, reaches its greatest frequency about the thirtieth year, diminishing rather slowly in frequency up until the sixtieth year of life. Cases in patients over sixty are rare, but occasionally cases are seen. In early adult life the chronic myelogenous form prevails, whereas in later years it is the chronic lymphatic type which is most often seen. The disease has a decided preference for the male, the ratio between the two sexes roughly is as 7 to 3.

A word in reference to the duration of the disease: probably because as a rule we recognize the disease in the late stages we find that the chronic types are of comparatively short duration—usually from two to five years after the recognition of the disease the patient dies from various causes. Probably if we recognized the disease earlier the duration would be found to be much greater than the usually recognized figures. Cases have been reported which have lasted up to as long as ten years. The acute types run a very rapid course, sometimes only a few weeks pass from the onset of the symptoms, which are definite and unmistakable, to the invariably fatal termination.

The signs and symptoms of leukemia are so well known when the condition is well advanced that it hardly seems necessary to dwell upon them any length of time. It is rare that the disease is recognized early. Last year I had the opportunity to see in consultation a case in which by routine blood count and differential count it was found that there were a small number of myelocytes in the blood-smear, about 15 per cent. The symptoms in this patient had only been present for a month or two. One would never have suspected that the leukemia, as we know

it, was the cause of these symptoms because, except for these blood changes, there was nothing else suggestive of it. Usually then the disease is far advanced or presumably so when we recognize it. Frequently the first subjective symptoms are that of the enlargement of the spleen which causes a heavy dragging sensation in the left abdomen. Subsequently the spleen may so enlarge as to cause extreme discomfort. On examination an enormous organ will be found which may fill the entire left side of the abdomen and which is associated with enlargement of the liver. In the lymphatic type we find that the spleen, as a rule, is very much smaller than in the chronic myelogenous type; also we were able to find on careful examination a thorough and wide-spread enlargement of the lymph-nodes throughout the body. The blood-picture is, of course, the diagnostic *sine qua non* in leukemia. The white cells are enormously increased, depending upon the type, the myeloid or lymphocytic cells predominating. In making studies of blood-smears there are two or three points I would like to dwell upon. The first is the necessity of recognizing the cell which is the precursor of the myelocyte, that is, the myeloblast. Very frequently these cells occur in the blood in small numbers and are called large lymphocytes. The differentiation is sometimes impossible without employment of the oxidase reaction, though usually when a well-prepared smear is carefully studied it is possible to find an irregular staining which is suggestive of beginning granulation.

There is one other phase of leukemia which is particularly interesting. I refer to the pathogenesis of the condition. Two theories have been advanced as to the cause of this disease. The first likens the disorder to a circulating sarcoma, and holds that the condition is in truth an evidence of the marked hyperplastic changes that occur in sarcoma. Those that believe in this theory hold that the rapid growth of the cells, the infiltration of the cells into the tissues, the hyperplastic changes in the bone-marrow and in the glands, and the course of the disease indicate a malignant disorder. On the other hand, there are those that contend that this disease is the result of bacterial infection. Certainly the acute cases of leukemia resemble, in their clinical

course at least, an acute bacterial infection. The febrile course, the tendency to hemorrhage, the marked prostration, are all suggestive of an acute infection. Furthermore, various bacteria have been isolated from the blood and tissues of persons suffering from leukemia, but none of these bacteria have been found capable of reproducing the disease in other animals, although fowl leukemia has been transmitted from one chicken to another. Transmission of the disease from one human being to another has not been reported, and leukemic mothers have given birth to normal children, two factors which would not be present if the disease were an infection. Furthermore, the types of leukemia vary very much more in relation to the age and sex of the individuals than they would were the disease a true infection.

In the treatment of leukemia we have nothing specific, but we do have a method of treatment which seems to enjoy very splendid results in the handling of the disease—radiotherapy. Radium and Roentgen ray both have the power of reducing the total number of circulating leukocytes, decreasing the size of the spleen, and materially improving the general condition of the patient, although no actual and definite cures have been reported as a result of this treatment. The results of Roentgen-ray treatment in the case I will show you are indicative of what can be accomplished by this method of treatment. If you are interested in the more exact description of the method of handling the disease I would refer you to the writings of Dr. Pancoast¹ who has made a very careful study of his cases which were treated by Roentgen ray. There is one other method of treatment which at one time was quite popular. That is the giving of benzol to these patients, on the basis of the discovery of Selling, that benzol is a leukotoxin and capable of reducing the number of circulating leukocytes. The results of the treatment with benzol have not been satisfactory probably because the drug has a deleterious effect on the other elements of the bone-marrow besides the leukocytic. While some men combine it with radiotherapy, it seems to us that more satisfactory results are obtained by the Roentgen ray alone.

¹ American Journal of Roentgenology, 1917, iv, 611.

I wish to present 3 cases of leukemia and to recite to you briefly the history of one other case which came under our observation the past year. These 4 cases present certain variations in the leukemic process itself, and it is, therefore, these variations and the result of treatment which I wish to show you, rather than to go into detail of their clinical course and their history.

Case I.—The first case I will be unable to show you, as the man died during the past winter, but he showed several interesting findings which I want to dwell upon briefly. The patient, G. W. M., male, aged forty-nine, came to the dispensary of the hospital complaining of weakness and insomnia. On February 19th his spleen had been removed at another hospital on account of its enlargement. Following this he had two transfusions and improved somewhat. The weakness, the enlarged spleen, and the anemia were the only complaints he had previous to having the spleen taken out. His condition, as far as we can trace it, was apparently about four years in duration, and the first subjective symptom he noticed was weakness together with the enlargement of his left hypochondrium. The spleen got so large that it filled his entire left abdomen. About two years ago he had Roentgen-ray exposure of his spleen, which became very much smaller under the influence of the treatment. About this time it was found that his red cells were 2,500,000; white cells, 14,000. His spleen was then removed. On admission to our dispensary we found that he had a red cell count of 3,350,000; white cells, 21,200, hemoglobin 69 per cent., lymphocytes 68 per cent. One myelocyte was seen, one nucleated red. There was quite a marked polychromatophilia. Subsequent counts showed very little change. Lymphocytes, as we then called them, ranged from 52 to 73 per cent. and white cells from 20,000 to 24,000. About two and a half months after admission his general condition was so bad that it was decided to refer him to the hospital in spite of the fact there had been little change in his blood count. His legs were edematous, the heart dilated, liver very much enlarged, and he showed signs of pulmonary congestion. He spent two months in the hospital and was

discharged feeling subjectively better and objectively decidedly better. He was readmitted again in about eleven days on account of marked dyspnea, listlessness, and nervousness. He rapidly became weaker and died shortly after his readmission.

Discussion.—In addition to the usual symptoms which occur late in the course of this disease there were two rather interesting points which I wish to dwell upon. The first is the fact that in our dispensary studies of the differential count we found apparently no abnormal cells, but a large absolute increase in the lymphocytes. However, when the patient was admitted to the hospital the oxidase stain was employed by Dr. Kearn, and it was found that these cells, which with the ordinary Wright's stain had a large bluish nucleus with homogeneous protoplasm, contained a large number of granules. Without this stain these cells, undoubtedly myeloblasts, would have been considered as lymphocytes. This is one point which I wish to bring up in differentiating between the chronic myelogenous leukemia and the chronic lymphatic leukemia. The next point is in reference to the differential diagnosis. This patient had his spleen removed at another hospital, where they evidently thought that he had a chronic malarial spleen with anemia. He had lived in Cuba for some years and for twelve years had had chronic malaria. Or else they thought they were dealing with Banti's disease. Apparently he was seen at this hospital at a time when his leukocyte count had fallen considerably and also when his spleen had been shrunken considerably by the Roentgen-ray treatment. In view of his intense anemia, enlargement of his liver, relatively low leukocyte count apparently physicians at this hospital thought that they were dealing with Banti's disease, nor was the pathologist in his report able to make a positive differential diagnosis between a leukemic spleen and the spleen of Banti's disease. The patient was seen in one of the aleukemic stages of his disease in which the count was apparently comparable to the normal count, and it is for this reason that it was evidently thought he had Banti's disease. There is often difficulty in differentiating the two conditions—Banti's disease and an aleukemic stage of leukemia. The aleukemia is a result

of certain factors; for example, we know that certain acute infections will produce a remission in the disease, or rather, I should say, a lowering of the leukocyte count, although the anemia still persists, and a return of the leukocyte picture to that of normal. At this stage the patient may present the signs and symptoms which make us think the patient is suffering with Banti's disease. Only a few weeks ago I saw a case at the Presbyterian Hospital in which the patient had a very large spleen and a mild degree of anemia and a leukopenia. It was a question whether we were dealing with leukemia in the aleukemic stage or whether this was a case of Banti's disease. The leukopenia which is usual in Banti's disease decided us in the view that we were dealing with Banti's disease. The patient was operated upon, and the spleen grossly resembled that of Banti's disease, but the organ was so adherent to the diaphragm that it was impossible to remove it. In spite of the fact that this first patient must have closely resembled Banti's disease, from the subsequent history it is perfectly evident that he had a leukemic spleen, and his later blood count made sure the diagnosis of leukemia.

Case II.—The next case I wish to deal with largely from the standpoint of treatment. This patient, a woman aged fifty-seven, first came under our observation in 1915, at which time we found nothing wrong on physical examination. Five years later she returned to us with a history of having lost 22 pounds in weight and complaining of severe pains in the abdomen. These pains started at the costal margin and went down to the pubis and were associated with diarrhea which usually lasted several hours. She was found to have an enlarged spleen on examination, and the glands of her neck and axilla were palpable, as well as most of the glands throughout her body. On account of the enlarged spleen a blood count was made, and it was found she had a hemoglobin of 70 per cent., red cell count 4,100,000; white cell, 369,000. She was followed for a few weeks at the dispensary, her blood count remaining about the same, varying from 369,000 to 472,000 white cells, with a differential count of from 89 to 99.5 per cent. lymphocytes. She was admitted to

the hospital on February 23, 1920, and there she was put under Roentgen-ray treatment. She was discharged a few weeks later and her blood count had fallen to 53,600, of which 94 per cent. were lymphocytes. Since this time in the past year and a half the patient was seen regularly at least once every two weeks. During this time her blood count has varied comparatively little. When her count goes up somewhat she is given further Roentgen-ray treatment and her count promptly comes down. But during this year and a half she has only had to have two series of treatment. The white cell count, for the most part, has been under 10,000, with a normal differential. Her general condition is extremely good; she has put on about 13 pounds in weight; she is up and around, able to carry on her work, and in every way in good condition. This case is interesting from the therapeutic standpoint. Roentgen-ray or radium treatment is said to produce only changes in the blood count, and is in no sense curative, but here we have a patient in whom the reduction of the white cells is accompanied by an improvement in her general condition and in her anemia. She can do very much more and in every way has been benefited by this treatment.

Case III.—The third case which I wish to show you is interesting because of the association of two rather unusual conditions, to wit, acromegaly and leukemia. This case has been reported elsewhere, so I will not go into the details of his condition. However, I might say that his acromegalic state commenced about eight years ago, with increase in the hands and feet. Within two years he was unable to hold his barber scissors on account of the large size of his fingers. His face and jaw also increased in size at this time. Apparently in the last eight years there has been no change in this condition. In addition to the symptoms of his acromegaly he has developed in the past few years weakness, swelling of his neck, and swelling of the glands throughout his body. Last April we found that he had a hemoglobin of 105 per cent., white cells, 88,000; red cells, 4,450,000. Differential count showed a large number of lymphocytes. This patient has also been on Roentgen-ray treatment, and whenever his count comes up is put under treatment again.

In April his count, as I said, was 88,000. One week later it was 51,300; the following week, 21,600; the next week, 14,800, and the next week, 19,100. By May 31st his total count was 19,600. During this period the lymphocytes averaged between 75 and 85 per cent. of the total number of cells. Counts made since then at intervals of approximately every two weeks have shown a total leukocyte count running between 8200 and 9000. His general condition has improved and he is decidedly more comfortable and able to be about and carry on his work.

Case IV.—I have still another case which I wish to mention very briefly. This little girl, aged seventeen, has myelogenous leukemia. She came to us only about a month ago, and here again her condition was not discovered until she had had a physical examination in which the doctor felt her enormously enlarged spleen. This organ extends almost down to the pelvis well out past the midline. Her blood count when we first saw her showed a well-marked anemia, white cells 59,200, and a large number of myelocytes. She has been started on Roentgen-ray treatment. The first count immediately after the Roentgen-ray treatment showed a white cell count of 54,000. A count made a few days ago shows a fall in two weeks to 14,500. It is a question whether a drop of this magnitude is not too severe. But she shows at the present time no untoward effect of this. Her subjective symptoms appear negative. She has no complaints; she says she feels strong and better than she has for some time.

CLINIC OF DR. GEORGE WILLIAM NORRIS

PENNSYLVANIA HOSPITAL

ACUTE TUBERCULOSIS AND CONDITIONS WHICH IT SIMULATES

Case I.—The first patient I have to show you today, a negress, twenty-four years of age, comes to us complaining of fever. She was perfectly well until a few weeks ago, at which time she went to bed on account of malaise and fever. She has had no gastric symptoms except anorexia and an attack of vomiting at the beginning of her illness. There has been no epistaxis. For the past week she has suffered from headache. She has had profuse night-sweats since the onset of her illness, also a slight, non-productive cough. She has had no circulatory or cardiac symptoms nor anything suggesting involvement of the nervous system. She has been bothered with nocturia two or three times nightly. Her menstrual history is unimportant except that she had one miscarriage some years ago. Other than this she remembers no illness. There has been no loss of weight. She does housework, is the mother of one child; food and hygiene have been fair, and the family history negative.

On inspection you will notice that she is well nourished and developed, that she lies quietly in bed, perspiring profusely, and appearing distinctly ill and toxic. Temperature $105\frac{2}{3}^{\circ}$ F., pulse 112, respirations 32. Her tongue is slightly coated, tonsils somewhat enlarged and cryptic. On the neck you will note several large, irregular scars resulting from former operations, presumably for tuberculous adenitis. We have suspected that she may have some pulmonary involvement because her expansion is none too good, and is perhaps especially limited on the right, also because the percussion note over the apices is impaired, breath sounds being bronchovesicular in character, especially

on the right, and occasionally crackling râles are heard on both sides. These râles are especially marked after coughing. Examination of the heart reveals nothing abnormal except an accentuated and split pulmonic second sound.

The *abdomen* is pendulous. There is slight epigastric tenderness to pressure, otherwise nothing abnormal is noted. The spleen is not felt.

Blood.—Hemoglobin 70 per cent., erythrocytes 4,500,000, leukocytes 6000 (polynuclears 70 per cent., large mononuclears 8, lymphocytes 20, transitionals 2).

Stool.—No occult blood and no ova, no parasites.

Widal Examination.—Negative.

Blood-culture.—Negative.

Urine-culture.—Negative.

Urine.—Amber, acid, 1004–1020, at times a trace of albumin, a few pus-cells, but no casts.

The temperature chart which I am passing around shows a continuous, maintained type of fever, ranging between 105.2° and 101° F. The pulse-rate ranges between 108 and 120; the respirations between 32 and 40.

From what disease do you suppose this patient is suffering? What conditions do we have to consider as possibilities?

A STUDENT: Typhoid fever.

DR. NORRIS: Yes, that would certainly have to be considered. The character of the fever, the mode of onset, the leukocyte count, and the absence of more definite signs in the lungs would be rather in favor of it, I think. On the other hand, the patient has had no nosebleed, the spleen has not been palpable, cultures made from the blood and urine have been negative, as has also the Widal examination.

With what other condition may we be confronted?

A STUDENT: Miliary tuberculosis.

DR. NORRIS: Yes, that is also a possibility. What examinations would you suggest to throw further light on the subject?

A STUDENT: The sputum.

DR. NORRIS: There is none.

A STUDENT: The spinal fluid.

DR. NORRIS: I think this is a good suggestion, despite the fact that our patient has had no symptoms of meningeal involvement. Can you think of anything further?

A STUDENT: Wassermann of the blood and spinal fluid.

DR. NORRIS: Yes, I think we should eliminate syphilis. It is possible that the patient might have a meningeal or cerebral type of this infection, although it seems less likely than the other conditions which have been mentioned. In the meantime our treatment will be purely symptomatic. Routine treatment for typhoid fever has been instituted.

(This patient was shown one week later. A Widal examination of the blood proved definitely positive for *Bacillus typhosus*. The fever began to break on the thirty-second day of the disease, and the patient made a slow and uneventful recovery, which was completed at a convalescent home.)

Case II.—Our second patient, a Hungarian laborer, forty-two years of age, comes to us complaining of abdominal pain and headache. These symptoms were first noted two weeks ago, at which time he was constipated, had a pain in the abdomen, and soon developed a high fever. This pain has continued, more or less, ever since, and is chiefly troublesome at night. It is very acute. Lately he has had additional pain in the right chest, which is increased by deep breathing, and he thinks he is now breathing more rapidly than was formerly the case. There has been no cough. His appetite has been poor, but he has never been nauseated nor has he vomited.

Past Medical History.—He states that he had typhoid fever four years ago, and that he was ill nine weeks at home. There is no history of venereal disease. His wife has never had any miscarriages. He drinks and smokes in moderation. In his early life he worked as a farm laborer, lately as a machinist in a sugar refinery. He has not been specially exposed to dust, and there has been no association with tuberculous individuals so far as he knows. Dr. Paul will read us the notes made at the time of his admission.

DR. PAUL: "The patient is a fairly well-developed but not especially well-nourished man, lying flat in bed. Respirations

are distinctly increased in rate (36 per minute). The patient is in considerable discomfort and appears quite toxic. Skin is very dry and hot. Face, expression quite anxious.

"Head.—No evidence of injury. Eyes: Pupils equal and react to light. Extra-ocular movements normal. Nose and ears negative. Mouth: Teeth in fair condition, slightly discolored. Pharynx very red, little or no exudate seen. Tonsils not seen.

"Neck.—No rigidity. Postcervical glands palpable and slightly enlarged. Thyroid not enlarged.

"Chest.—Fairly well developed. Long and quite flat. Walls not thick. Expansion fair. Costal angle normal and moves out well with inspiration. Expansion apparently equal on both sides. Supraclavicular fossa quite deep.

"Anteriorly the percussion note is resonant, a few inspiratory crackles are heard at the left base, but no apparent change in breath sounds.

"Posteriorly the lungs are normal to percussion, fine subcrepitant râles heard at both bases on inspiration.

"Heart.—Considerably enlarged. P. M. I. is seen in the sixth interspace $14\frac{1}{2}$ cm. from midsternal line. A thrusting impulse is felt here. No thrills. The cardiac dulness extends 13 cm. to the left of the midsternum in the fourth interspace and 4 cm. to the right. The first sound is rumbling in quality and quite prolonged, second sound sharp. At the base the sounds are barely heard.

"Abdomen.—Walls are not thick; it appears sunken. No rigidity, no distention. Liver edge is palpable 7 cm. below the costal margin in the midclavicular line, and 8 cm. below the ensiform. Spleen is not felt. No tenderness present. No masses. No peristalsis heard on auscultation.

"Extremities.—Negative, except for the presence of many pigmented scars over the lower shins, especially marked on the right leg.

"Pulses.—Rapid, but fair quality. No dicrotism.

"Reflexes.—Biceps and triceps knee-jerks are present, but not active. No clonus. No Babinski. No Kernig."

DR. NORRIS: At the time of his admission his hemoglobin was 48 per cent., erythrocytes 5,280,000, leukocytes (several estimations) 3100 to 3200. Of these, polynuclears 64; lymphocytes 12; small lymphocytes 4; transitionals 20. *Blood*: Wassermann negative. Widal negative. The urine showed a trace of albumin and a few hyaline casts.

In looking at the patient today you cannot but be impressed with the fact that he looks seriously ill and very toxic. You will further note that although polypnea is striking, dyspnea is not causing discomfort. Percussion discloses a marked impairment of the right lower chest, both posteriorly and laterally. Over this area the vesicular murmur is diminished, has a slightly bronchovesicular quality, and is associated with many fine and coarse crackling râles. The spleen is still not palpable, although the liver can be readily felt. The dulness over the right chest is a recent development. A few days ago I made the following note: The left chest is smaller than the right, and expansion over its upper portion much diminished. Below the clavicle on the left side there are numerous fine respiratory crackles and distinct diminution of the vesicular murmur.

I would like to read you Dr. Bowen's radiographic reports: "There is in the right chest a rather uniformly mottled shadow, the greater portion of which is perhaps due to pneumoconiosis, but there is in the left apex a marked local increase in density. There are distinct adhesions between the pericardium, the diaphragm, and the left parietal pleura."

Glancing at the temperature chart, you will note that at the time of admission the temperature was 103° F., pulse 124, respirations 36. This was followed by a gradual decline to normal one week later, with symptomatic improvement, and discontinuance of the "sponges" which he had been getting. Later there was a sudden rise in temperature from 99° to 104.2° and 104.3° F. Following this the temperature remains high, is uninfluenced by sponging, and associated with an increase in both the cardiac and respiratory rate.

Comparing this patient with the negress first shown, you will note certain similarities and certain differences both in the

history of symptomatology and physical findings. Have you any suggestions regarding diagnosis?

A STUDENT: Miliary tuberculosis.

DR. NORRIS: Yes, I think so, but upon what do you base your opinion?

A STUDENT: The history of preceding typhoid fever, regular onset with progressive symptomatology and physical findings, leukopenia, negative Widal's.

DR. NORRIS: Yes, most of those points are well taken, although leukopenia suggests typhoid fever rather than generalized tuberculosis. In addition, we have to consider the fact that the spleen has not been enlarged, and that the polypnea is out of all proportion to the physical findings in the chest and to the respiratory discomfort. We have been treating this patient along "typhoid lines," hoping that he might have this disease, but fearing that he is suffering from generalized tuberculosis.

(This patient died several days later from gradual exhaustion associated with an increase of physical signs, chiefly râles in the chest. No autopsy was permitted, but the diagnosis of general miliary tuberculosis seems to be entirely justified. The x-ray findings were strongly corroborative. This method of examination should, if possible, always be made in cases of suspected miliary tuberculosis.)

Case III.—The third patient is a farmer, twenty-six years of age, whose chief complaint is headache, of four days. He was admitted fourteen days ago.

Present Illness.—Five days before admission the patient went to bed feeling poorly. The next day had severe, paroxysmal knife-like pain in the occiput, for which medication was not efficacious. The pain continued, while his neck and back became stiff. Sleep was impossible. There were no other symptoms.

Past Medical History.—Always healthy. Served with our Army in France. Denies venereal disease. Wife has had no miscarriages.

Physical examination revealed nothing of moment except palpable epitrochlear lymph-nodes; suggestive tache cérébrale, sluggish knee-jerks, cervical rigidity, but no Kernig's sign.

The data thus far suggested: (1) some form of meningitis; (2) cerebrospinal lues.

Two lumbar punctures which yielded clear fluid (20 c.c.) under normal pressure failed to relieve the headache.

The headache continued, the cervical lymph-nodes became enlarged, the tongue heavily coated.

Ophthalmoscopic Examination (Dr. W. T. Shoemaker).—Poorly defined disk with enormously distended veins "very suggestive of intracranial disturbance."

Spinal Fluid.—Globulin 0, sugar \pm , 7 cells per cubic centimeter (lymphocytes 3). Wassermann negative.

Blood.—Hb. 75 per cent. Erythrocytes 5,000,000. Leukocytes 9000.

Urine.—1010, acid, albumin 0, glucose 0, few hyaline casts, acetone 0, diacetic acid 0.

Temperature.—103° F., respiration 28, pulse 76.

Ten Days Later.—The headache and cervical rigidity persisted. Fluoroscopy of the chest and head (for sinus infection) was negative. Examination of the nose and throat (Dr. Davies) negative. Ophthalmoscopic examination shows persisting venous distention and tortuosity.

Lumbar puncture at this time showed 40 cells (90 per cent. lymphocytes) in a clear fluid under normal pressure.

Four days later the patient became wildly delirious, requiring sedatives and physical restraint.

Rigidity of the neck became extreme, the right eye ptosed, and numerous râles were audible in the lungs, especially in the left axillary. The temperature course was irregular and intermittent (98° to 104° F.), but both pulse and respirations remained slow (80 and 24 respectively).

A diagnosis of tuberculous meningitis was made at this time.

As you look at this patient today he seems well and comfortable. He has gained 15 pounds in weight, and tomorrow (two months after admission) he is to be discharged—recovered!

What did he have? Surely some form of meningitis. Certainly it was not due to the meningococcus, and with almost equal certainty, not to the *Spirochæta pallida*. Was it the

TABLE I
SPINAL FLUIDS

Case No.	Appearance.	Pressure.	Total count.	Poly.	Lym.	Other.	Fehling's.	Culture.	Wass.	Organisms.	Glob.
99	Clear	++	280	5	95	0			Neg.	0	+
57	Slightly turbid	++	36	4	96				Neg.	0	
97			40		65	1			Neg.	0	
79			300 to 332	2	97						
59			600	25	75						
6				2	98				Neg.		+
27					Large 70					T. b. +	
31					(Chiefly lymphocytes)						
39											
37											
32	Clear									T. b. +	
1	Clear									T. b. +	
43	Clear									T. b. +	
44											
25	Slightly turbid									T. b. +	
46	Clear									T. b. +	
93										T. b. +	
52	Clear			2	98	0				T. b. +	+++
87					(Many polys., few lymph.)						
92					Negative						Post.
97			520	70	Polys. ++						
92			140	90	Polys. ++						
97			500	90	Polys. ++						
67			70		(Small lymphocytes ++)						
89	Slightly turbid	++	32							T. b. +	
26	Clear									Neg.	
38	Slightly turbid									T. b. +	
5	Cloudy (no other note)	— several monos. per fld.	66 to 288 cells per cu. m.m.								+
56											
80	Slightly turbid		250	78	18	4					
71			250	20	80						
65	Clear		460						Neg.	No.	Polynucleosis.
77	Slightly turbid	++	440	4	96				Neg.	Neg.	P. M.
61										Neg.	P. M.
85			500	12	88	(Increased lymph., occ. poly.)				Neg.	P. M.
54	Clear		65		93	0					
82		++	180	7	(Mostly lymphocytes)						
55			16		100					T. b. +	
24	Bloody				100					Neg.	
										T. b. +	P. M. G. P. neg.

[illegible]

tubercle bacillus? No such organisms were ever demonstrated in the spinal fluid and, unfortunately, animal inoculations were not made.

Further, you will say that people do not recover from tuberculous meningitis. In the vast majority of cases this is true, for tuberculous meningitis is usually but part and parcel of a general miliary invasion, and at autopsy the body is usually more or less riddled with tubercles, but careful study of the literature shows that in all some 40 cases of undoubted tuberculous meningitis have been known to recover.¹

Our final diagnosis, therefore, must be written "serous meningitis," inasmuch as the etiologic fact remains undiscovered. But our patient was not alcoholic, not syphilitic, and not intoxicated by a deranged metabolism, and I personally believe that he represents one of those rare cases of tuberculous meningitis that do get well.

The cases which you have seen today represent relatively common diagnostic stumbling-blocks. Perhaps such cases will so continue, but certainly mistakes will less frequently be made if we maintain a healthy skepticism when we are dealing with cases of suspected typhoid fever, atypical pneumonia, cerebrospinal syphilis, meningitis, or uremia; and if we bear in mind the fact that generalized tuberculosis may masquerade in many forms.

Dr. Farley² has recently completed a statistical study of acute tuberculosis based upon 100 cases, 40 of which were autopsied. The charts upon the wall are the results of his work. The first (Table I) shows the results of the spinal fluid examination in 74 cases. You will see that the cell count ranged from 16 to 720 and that tubercle bacilli were demonstrated in about 50 per cent. The fluid was clear with great frequency, but in two instances it was cloudy, and in three others (4 per cent.) it contained pus-cells instead of the usual mononuclear variety.

¹ Hollis and Pardec, *Arch. Int. Med.*, July, 1920, 26-49.

² Norris, George W., and Farley, D. L., *Acute Tuberculosis: An Analysis of 100 Cases from the Pennsylvania Hospital and the Hospital of the University of Pennsylvania*, *Pennsylvania Medical Journal* (to be published 1922).

The other chart (Table II) shows the distribution of the lesions postmortem.

TABLE II

		(+) Per cent.	(-) Per cent.
1. Viscera of the chest, tuberculosis lesion in	36 cases	(90), none	4 (10)
2. Abdominal viscera,	32 "	(80), "	8 (20)
Individual organs:			
1. Lungs, some form of lesion,	32 "	(80), "	8 (20)
2. Lungs, miliary lesions,	29 "	(72.5), "	11 (27.5)
3. Lungs, ulcerative or caseous lesions,	21 "	(52.5), "	19 (47.5)
4. Meninges,	31 "	(77.5), "	9 (22.5)
5. Spleen,	24 "	(60), "	18 (40)
6. Liver,	23 "	(57.5), "	17 (42.5)
7. Pleuræ,	22 "	(55), "	18 (45)
8. Kidneys,	18 "	(45), "	22 (55)
9. Intestines,	16 "	(40), "	24 (60)
10. Ulcers of intestines,	11 "	(27.5), "	29 (72.5)
11. Peritoneal lymph-nodes,	9 "	(22.5), "	31 (77.5)
12. Adrenals,	7 "	(17.5), "	33 (82.5)
13. Omentum,	6 "	(15), "	34 (85)
14. Heart and pericardium,	6 "	(15), "	34 (85)
15. Pancreas,	5 "	(12.5), "	35 (87.5)
16. Testicles and epididymis,	4 "	(10), "	36 (90)
17. Urinary bladder,	3 "	(7.5), "	37 (92.5)
18. Prostate,	3 "	(7.5), "	37 (92.5)
19. Stomach,	1 "	(2.5), "	39 (97.5)
20. Larynx,	1 "	(2.5), "	39 (97.5)
21. Thoracic duct,	1 "	(2.5), "	39 (97.5)
22. Diaphragm,	1 "	(2.5), "	39 (97.5)
23. Aorta,	0		40
24. Gall-bladder,	0		40
25. Skin,	0		40
26. Retina probably not examined in most cases.			

The type of fever varied. It was typhoid-like in 48; irregular in 39, and normal or subnormal in 7.

It was interesting to find that the spleen was palpable in only 3 per cent. of the cases.

Certain other points disclosed by Dr. Farley's study deserve emphasis. Let me briefly epitomize them:

The x-ray examination should, if possible, always be made. The most common physical signs in the lungs were hyper-resonance, râles, and short pleural frictions. In 90 per cent. of the cases an active tuberculous lesion was found in the chest.

Only one-third of the patients having meningeal involvement stressed headache as their chief complaint. Epistaxis occurred in 9 per cent of these cases. Vomiting was noted in 40 per cent. and convulsions in 12 per cent. of all cases. Abdominal pain was noted only six times, although 80 per cent. of the cases showed tubercles of the subdiaphragmatic viscera. General adenopathy occurred in only 5 cases. Cervical rigidity was a more reliable sign of meningeal involvement than Kernig's sign. Retinal abnormalities—neuroretinitis, hemorrhagic retinitis, optic atrophy, etc.—occurred in 8 per cent. No retinal tubercles were encountered. (I have personally seen one case in which the diagnosis was established by a retinal tubercle. Although evidently of rare occurrence, these lesions should be sought for.) Leukocytosis is the rule—a white count below 5000 occurred only five times in 128 estimations. (Leukopenia is more common and leukocytosis more rare in typhoid fever.) The von Pirquet test (11 cases) was negative in 10, the explanation generally accepted being that a system overwhelmed with toxin does not react.

The cases which we have shown today present some useful lessons. The first was a case of typhoid fever in which the diagnosis of acute tuberculosis was at times under consideration; the second case appears to be a generalized tuberculosis with an onset and numerous findings strongly suggestive of typhoid fever. The third is a case of meningitis having most of the characteristic features of the tuberculous variety, but terminating in recovery.

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POSTOPERATIVE PULMONARY COMPLICATIONS, WITH 3 ILLUSTRATIVE CASES

STATISTICS have been published which seem to show that irrespective of the operation performed or the anesthetic employed, 1 patient in every 50 operated upon will develop some postoperative complication, and, furthermore, 1 patient in every 150 or 175 operated upon dies as a result of a postoperative pulmonary complication. Even if these statistics, as is so often the case, exaggerate the point in question, yet there can be no doubt that postoperative pulmonary complications are both amazingly frequent and severe.

The internist usually is called in after the complication has developed, and on him is then placed the responsibility of diagnosis and therapy. Often the internist is handicapped by the surgical dressings or by the impossibility of turning the patient for an examination of the lungs posteriorly. Furthermore, medical, as opposed to surgical, matters have usually been somewhat neglected in the preoperative history and examination, and finally, the whole picture is confused by the results of the operation and perhaps by the condition for which the operation was performed. One is dealing with a patient who may already have fever and leukocytosis; who may already have been suffering severe pain; or who may be in a condition making subjective symptoms unobtainable.

The importance of proper diagnosis is obvious. For example, the patient's life itself may depend upon the decision as to whether certain symptoms are the result of a pulmonary complication or of a local complication in the site of the surgical

procedure. Again, much may depend upon the differentiation of one pulmonary complication from another. Fatal delay may occur if a pulmonary abscess or an empyema is temporized with, under the mistaken diagnosis of postoperative pneumonia or tuberculosis.

Granting the importance and difficulty of diagnosis in this group of cases, it behooves us to consider the factors which tend to bring about pulmonary complications, the methods of their development, and the symptoms and signs which characterize them.

Of the factors which lead to pulmonary disturbance after operation, three have been especially emphasized: partial collapse of the lung, embolism or infarction, and direct pulmonary irritation or infection. Similar end-results have been attributed by different writers to each of these various factors, and they have each been emphasized at the expense of the others.

Collapse of a part of one or both lungs as an initial cause of postoperative pulmonary complication was emphasized by Pasteur some years ago, and more recently by Briscoe. The latter believes that the majority of pulmonary conditions which give rise to anxiety after operation are dependent upon, or influenced by, deflation of some area of pulmonary tissue. He considers that the collapse of the lung is a consequence of prolonged supine position. Others have advanced the view that the collapse occurs only in cases where the operation has resulted directly or indirectly in a fixation of the diaphragm. Certain it is that the collapse usually involves the lower lobes, and also that pulmonary complications are especially frequent after upper abdominal operations.

The deflation occurs soon after the operation, but is often unrecognized because it gives few or no symptoms. A half-hearted cough and a little expectoration may be its only manifestations. In other instances, however, an inflammatory process originates in the collapsed area and proceeds to produce the picture of a bronchopneumonia with perhaps some pleurisy and pain. With this inflammatory process there occurs fever.

At this stage the picture presented is that of the usual postoperative pneumonia and there is no sure evidence that the process commenced with a pulmonary collapse.

It is claimed that a more or less massive collapse may suddenly occur usually in one of the lower lobes. A sharp attack of dyspnea with cyanosis and a rapid, weak pulse is said to usher in such an attack. There occurs pain over the lower chest and in the substernal region. The patient may be *in extremis*. On examination the lower lobe of one side is found collapsed and inactive; the opposite lung is overactive. Over the affected lobe there may be retraction of the interspaces, impairment to percussion, weak tubular breathing, and an absence of vocal fremitus and râles. The only sure sign, however, is said to be a displacement of the apex of the heart toward the affected side. Fever appears, but the whole attack is usually over within forty-eight hours, and is seldom, if ever, fatal.

Such an attack due to postoperative collapse of the lungs the author has never seen, and he is inclined to the belief that embolism and not collapse is responsible for most of these serious sudden attacks. On the other hand, deflation, or at least inactivity of the lower lobes, undoubtedly occurs after many upper abdominal operations, and this may be the starting-point of many of the inflammatory basal troubles which develop in such cases. Collapse of the lung will, of course, occur if the chest cavity is opened, as, for example, during an operation for carcinoma of the breast.

Embolism.—The second factor which may initiate pulmonary disease during the postoperative period is embolism from the operative area. This may occur after any operation and is predisposed to by marked tissue trauma, by infection, and by movability of the part. Operations on tissues with very free venous supply are especially likely to give rise to this trouble: laparotomy and operations upon the female genital system give perhaps the highest figures.

According to the size of the embolus and, therefore, of the occluded pulmonary vessel the symptoms vary in severity. In this respect a somewhat confusing nomenclature has arisen;

the term "infarction" is used of the results of small particles broken free from the clot in the veins near the operative field, while the term "embolism" is applied to the lodgment of larger emboli. Used in this sense, infarction is a much milder condition than embolism. It is the gynecologists who have especially emphasized this group and most of the statistical figures are based on series of gynecologic cases. References to several such articles are given at the end of this clinic.

Infarction in three-quarters of the cases does not occur until the second or third week of postoperative convalescence, but, as a rule, this convalescence has not been wholly normal. Usually there has been a little daily elevation of temperature, and in about one-quarter of the cases a thrombophlebitis in the femoral vein has been recognized for a few days before the lung disturbance develops. *On the day of infarction the fever rises a little higher and the patient complains of pain in the lower chest, much more often on the right than on the left. There is apt to be some little cough, and perhaps some dyspnea and even hemoptysis, but these two latter are much less evident in this group than with true embolism.*

On the first day the diagnosis is apt, incorrectly, to be pleurisy, and this is apparently confirmed when on the second day the fever is still higher and a friction-rub can be heard over the affected base. Still later râles appear, and there may be some little dulness to percussion and suppression of breath sounds. The whole process is over within a week unless a repetition of the infarction or a true embolic attack develops. Recovery is complete in the vast majority of cases, and no residual signs remain in the lungs. At the height of the attack the roentgenogram will show a shadow, and the laboratory will report a moderate leukocytosis. Occasionally the process eventuates in a more serious localized infection resulting, for example, in abscess.

Embolism, as opposed to infarction, occurs in the same group of postoperative cases, but usually between the sixth to the tenth day after operation. It is a much more alarming and tragic happening; half of the cases die within a half-hour.

The onset varies considerably; occasionally death occurs almost at once from suffocation; in other instances different groups of symptoms may predominate. At times hemoptysis and substernal oppression may be the chief symptoms. occasionally cerebral disturbances, such as convulsions, paralysis, or coma, may easily lead to a mistaken diagnosis. High fever is common and circulatory collapse is not infrequent. The weak, running pulse, rapid breathing, and clammy skin of shock are often present. Those who survive the initial attack gradually recover, or succumb to a second embolism. If the embolism was not sterile, abscess or gangrene may ensue. Not all cases which present the picture of fatal pulmonary embolism prove to be of this nature at operation. Capelle has reported a number of instances where the clinical diagnosis was postoperative pulmonary embolism, but at autopsy no pulmonary embolism could be found, and death had apparently been due to the failure of a fatty degenerated heart.

Direct Pulmonary Irritation or Infection.—This third factor is the one which formerly received the greatest attention and which was thought to explain the majority of postoperative pulmonary complications. The modern tendency is rather too much in the opposite direction. Incident to anesthesia and operation a number of insults may be offered to the lung. The anesthetic itself is irritant; infected material may have been aspirated during the period of unconsciousness; the lung may be traumatized; congestion and stasis may occur in the lung from failing circulation, or as a result of deflation of the lung from collapse or from fixation of the diaphragm. All of these factors would tend to prepare the soil for the establishment of a new infection or for the spread of one previously existing, as, for example, bronchitis and, probably indirectly, tuberculosis.

The postoperative infection which results from one or other of these factors may vary very much in severity. Whipple believes that what is usually called a "postoperative reaction" is, in fact, a postoperative pneumonitis or mild pneumonia. It occurs within forty-eight hours after the operation with a

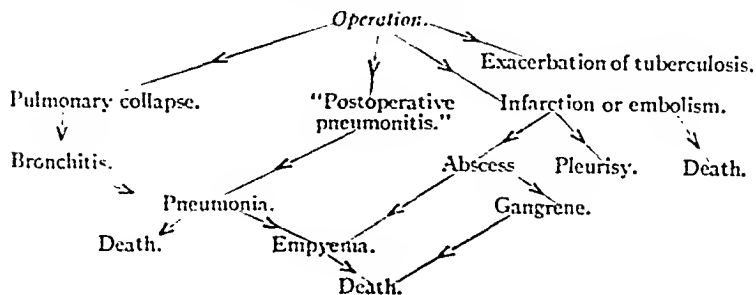
sharp rise of temperature, but no chill; there is moderate cough and pleuritic pain. Dulness can be demonstrated over an area at the base of a lung and over this area the breath sounds are diminished. A little later bronchial breath sounds may appear. At this stage the roentgenogram shows a shadow. The temperature returns to normal in two or three days and the only unfortunate result, as a rule, is a delay in convalescence. The condition is seldom fatal, but may be the starting-point for more serious infective processes. In most of the cases a Type IV pneumococcus is found in the sputum.

An extensive bronchitis may follow any operation under general anesthesia and a typical pneumonia either of the lobar or bronchopneumonia type may, of course, develop. Little need be said about these other than that the true lobar form is rare. It should, however, be emphasized that the spread of tuberculosis which sometimes appears after anesthesia is probably due to the occurrence of a non-tuberculous pneumonitis in the tissues surrounding the tuberculous foci, and the extension of the tubercle into the tissues softened by the secondary infection. Aspiration of infected sputum or pus may originate a pneumonia which will usually appear within a few days after the operation.

There is one group of postoperative cases in which it is an unsettled question whether the frequent occurrence of pulmonary abscess is due to aspiration of infected material or to the lodgment of septic emboli. These are the cases in which pulmonary abscess follows an operation on the mouth or throat. One of the illustrative cases chosen for this clinic is of this type. Often the operation is no more extensive than the extraction of a tooth or the removal of the tonsils; often no anesthetic has been employed. After the operation convalescence apparently proceeds normally, but after a few days cough and an irregular fever develop. With surprising constancy the end of the second week is the time when a free evacuation of purulent sputum begins, and the presence of the abscess is for the first time recognized. By some it is claimed that these cases result from septic emboli leaving the operative site and lodging in the

lung. The time of occurrence is the same as that of the cases of infarction, but these posttonsillectomy cases show no manifestations of the lodging of the minute embolus, and a far greater tendency to abscess formation. On the other side are those who believe that aspiration of infected material is the cause of the trouble, and some claim to avoid this complication by carefully preventing every possibility of aspiration. If due to aspiration it is difficult to picture the process which proceeds with so few symptoms during the first ten postoperative days. It is easier to imagine a very small but highly septic embolus gradually producing an abscess in the lung, walled off at first, but rupturing about the end of the second week. Such cases often go on to further complications, such as gangrene or empyema.

This brief review of this subject shows us at once that not only do different writers emphasize different factors as the probable cause of similar end-results in postoperative pulmonary complications but also that many borderline cases must occur which fall between the various types described. Perhaps the following diagram will help to show the various possibilities. Of course, at any point the process may be arrested and cure occur; the diagram is merely intended to show how the end-results may be arrived at by various routes. Perhaps more than one factor may be active in a single instance, or perhaps the different factors described are merely parts of a whole. For example, there is a striking resemblance between the manifestations described under the headings Collapse and Postoperative pneumonitis, also in their course and results. Perhaps they are identical, or at least associated together in many instances.



Illustrative Cases.—The 3 patients whose case histories are to be presented were all in the University Hospital within a short time of one another. They are selected for presentation in clinic because each presents points of special interest.

Case I.—J. W., colored, male, age thirty-two years. Admitted with the chief complaint "pain in the loin and bloody urine." Renal calculus was diagnosed and confirmation was obtained by roentgenogram. Left nephrolithotomy was performed under ether anesthesia and two renal calculi were removed. He made an uneventful recovery and the temperature did not rise above 99° F. from the fifth to the fifteenth postoperative day. On this latter date the stitches were removed in the morning; at 8 P. M. the patient was suddenly seized with severe sharp pain on the right side, near the level of the umbilicus and radiating to the right chest and shoulder. His respiration was noted to be shallow and rapid; the pulse reached 96 and the temperature 99.6° F. The next morning the patient coughed up several "lumps of blood" and the signs of acute pleurisy were discovered at the right base; fever a little higher. Two days later the patient felt much better, the temperature was lower, but signs at the right base included impairment to percussion, diminished breath sounds, egophony, and pectoriloquy. Exploratory puncture was performed, with negative results. From this date on the evidences of pulmonary trouble grew less and less clear and convalescence proceeded rapidly. Two weeks afterward a fluoroscopic examination revealed nothing but an adherent right diaphragm, probably residual from the recent attack.

This case is a typical instance of so-called "postoperative pulmonary infarction" or mild embolism. It was unusual in the operation which it followed, and in the possible relation of the attack to the removal of stitches. The signs which led to the unnecessary puncture of the pleura were probably the result either of fixation of the diaphragm by the pleurisy with some deflation of the lung, or of a pneumonitis around the site of the infarction.

Case II.—Mrs. K. S., white, aged thirty-eight years. Patient

had been in perfect health until three weeks before admission, when she had nineteen teeth extracted under nitrous-oxid anesthesia. On recovering consciousness she vomited and coughed up considerable blood, and she states that she noticed a rattling sound in her chest. Her mouth was very sore for the next few days, but she had no other symptoms until the eighth day after the operation, when she developed a "catchy pain" near the tip of her left scapula. Two days later, the tenth post-operative day, she commenced to cough and spit up bloody purulent material. This continued and was always worse in the early morning, but she never brought up any large amount of pus at a single time. The sputa had a very offensive odor.

On admission three weeks after the dental extractions she was found to have abnormal physical signs at the base of the left lung; there was over this area a prolongation of the expiratory element of the breath sounds, and many râles were heard at the end of deep inspiration. The sputum was purulent and contained no tubercle bacilli. There was fever up to 102° F. and a leukocytosis of 19,600, with 92 per cent. of polymorphonuclear cells. A diagnosis of lung abscess was made. The roentgenographic findings were somewhat confusing, as "very marked prominence of linear markings throughout both lungs" was reported. Probably the major part of the lesion which we recognized on physical examination was hidden behind the heart shadow.

With rest in bed, postural drainage, and the use of an autogenous vaccine made from the sputum cultures the patient rapidly improved, and was discharged free of fever and with practically no cough or expectoration. Her improvement continued for some time after leaving the hospital, but about a month later the cough again became severe, expectoration of purulent material recommenced, and she began to have occasional night-sweats. Three months after leaving the hospital she developed a severe "piercing, cutting pain" in the left side, fever, and hemoptysis, and she returned to the hospital. On this admission all the signs of empyema were found at the base of the left lung, and by a needle introduced in the eighth

interspace in the posterior axillary line thick greenish, blood-tinged pus was obtained. The fever was high; the leukocyte count 23,500. The next day a resection of the seventh and eighth ribs was performed. A large amount of bloody purulent material was evacuated from what appeared to be a localized empyema possibly of interlobar origin. Unfortunately the patient did not recover from the operation.

This case is a good example of the pulmonary complications which occasionally follow operations on the nose, mouth, or throat. The statement of the patient, that she coughed up blood immediately after the operation and that she noticed a rattling in her chest, would seem to support the theory that the aspiration of infected material is the cause of the lung complication. The onset of the cough and expectoration occurred according to rule, about the tenth day, and from then on the case behaved as many of them do. The possibility of a tooth having been permitted to fall into the lung was considered, and special roentgenograms were taken to rule out this cause of pulmonary trouble.

Once an abscess is formed in such cases the condition is serious, and at best is of long duration. We were amazed at the rapid improvement which this patient exhibited, but the later happenings confirm the accepted view that pulmonary abscess is slow to heal and often leads to serious danger. With improvement in the technic of pulmonary surgery, operation is more and more becoming the accepted treatment for abscess of the lung, unless medical treatment is promptly successful.

Case III.—I. B., female, white, aged sixty years. Two weeks before admission to the hospital the patient developed a small infected pimple on the lateral palmar aspect of the second finger of the right hand. This progressively grew worse despite local treatment. By the time the patient entered the hospital the infection had extended up to the elbow. Except for the local infection the physical examination was negative; the temperature was irregular and varied between normal and 102° F.; the pulse-rate and respiratory rate were normal.

Before admission the finger had been incised, but the further

spread of the infection required freer drainage, and this was performed soon after admission. Four days later the fever, which had never entirely subsided, became higher and more constant. On the sixth day following the second operation the patient complained of pain in the left side of the chest. the pulse became more rapid, and the respiratory rate rose to 40 per minute. The condition of the hand and arm had not improved and further incisions for drainage were made. Following this the patient seemed to improve somewhat; the local infection seemed better. The temperature, pulse-rate, and respiratory rate all approached normal. The improvement, however, was of short duration, and a week following the third drainage operation the patient rather suddenly grew worse again. My examination on that day revealed the entire left lung consolidated with but little air entering it; the opposite lung was overactive. The temperature was 103° F., pulse-rate 120, respiratory rate 44 per minute. Leukocyte count was 17,000; sputum of chocolate color, under the microscope bacteria, pus, and blood were seen; no tubercle bacilli or elastic fibers were found. The diagnosis suggested was "pulmonary embolism with secondary pneumonia and perhaps abscess."

Two days later the patient appeared a little better; the left base was somewhat less impaired and more air was entering it. The improvement was not sustained and the patient died two days later.

Autopsy revealed "embolic pneumonia of left lung with multiple abscess formation"; the left pulmonary artery was thrombosed. The left pleural cavity and the pericardium both showed an acute fibrinoserous inflammation. A recent infarction of the spleen was discovered. Cultures of the heart's blood gave a pure growth of a hemolytic streptococcus; cultures of the lung abscess and smears from the pericardium revealed apparently the same organism.

Discussion of this case is made difficult by the uncertainty concerning the chronologic sequence of events. It is probable that a septic embolus lodged in the lung on or about six days after the operation for freer drainage, which was performed

soon after admission to the hospital. The later increase of symptoms was probably coincident with a development of pneumonia around the infective focus. Of course, this case is open to other interpretations and perhaps the case should not be included under the heading of postoperative complications. It is closely allied, however, and in my opinion belongs in the group of pulmonary complications incident to the spread of infection from an operation site by venous embolism. In this instance the embolus must have been very minute, for the symptoms of lodgment were insignificant, while the results of the infection dominated the picture.

Conclusion.—Many more cases might be detailed, but it is unnecessary to burden you with them. They represent the better known varieties of pulmonary complications occurring after operation. You are all familiar with the tragic picture of sudden pulmonary embolism, and you are even better acquainted with what Whipple calls "postoperative pneumonitis."

It is important, however, to keep in mind the various factors which have been emphasized as favoring the occurrence of postoperative complications in the lungs, in order that efforts may be made to avoid them. The following suggestions may be used as a starting-point in outlining preventive measures. Others which are directly related to the operation and surgical aspects of the cases are not mentioned:

(a) The preoperative examination of the lungs should be more than cursory. The findings of any abnormal signs in the lungs should lead to thorough investigation before operation, unless an emergency exists. Occasionally a careful chest examination will prevent a needless operation, as, for example, the finding of a basal pneumonia in a patient supposed to have acute appendicitis.

(b) If immediate operation is necessary in a case with upper air passage infection, the anesthetic of choice is either nitrous oxid-oxygen or local anesthesia. At operation the anesthesia should be for as short a period as possible; every effort should be made to prevent aspiration of infected material or foreign bodies.

(c) The patient should not be kept in the supine position any more of the time than absolutely necessary during the first few days after operation.

(d) Deep breathing to move the diaphragm and expand the pulmonary bases should be encouraged as soon after operation as possible; and several times a day for at least three days.

(e) Alert watchfulness for evidence of thrombophlebitis, especially in the femoral veins. Absolute rest to be insisted on for several weeks if thrombophlebitis is discovered.

(f) Period of convalescence in bed must be varied according to the operation, the patient's general condition, and the type of complication to be feared. If deflation of the lower lobes is threatening the patient may perhaps be better out of bed, while if embolism is feared a protracted stay in bed may be indicated.

(g) It would be an ideal arrangement to have an internist on duty in the surgical wards of a hospital for the purpose of improving the preoperative examination of patients, and of assisting in their postoperative care.

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DUST SENSITIZATION IN BRONCHIAL ASTHMA

Dust plays an important part in bronchial asthma. Of the exciting causes it is by far the most usual. The motes seen floating in the sunbeam entering a dark room testify to the almost universal presence of dust. One can, therefore, readily understand how in an asthmatic patient, at a time when there is bronchial infection and a congested mucosa, together with a "hair-trigger" vasomotor system, the inhaled dust, acting simply as a mechanical irritant, can precipitate an attack of asthma.

It is, however, a significant fact that the dusts to which we are exposed are commonly of an organic nature. They contain varying amounts of protein, and may, therefore, act as antigenic substances in producing a true protein sensitization. This fact has been well recognized. Dust sensitization in one form or another is known to be the commonest single cause of allergic types of asthma as seen in adults. The common forms of sensitization to epidermal substances, such as horse dander, cat hair, dog hair, chicken or goose feathers, are really cases of dust sensitization. It is true that, as a rule, such dusts are present in a concentration sufficient to cause trouble only in the immediate neighborhood of their source, and some patients are permanently relieved by simply avoiding contact with a feather pillow, by removing the offending animal pet from the house, by staying away from horses, etc. But often the room in question has been thoroughly saturated with the offending dust, for example, feather dust in a bed-room. Every time the room is

¹ From the Medical Division of the University Hospital.

swept or the bed made the air is filled with the specific dust, and not until such a room has been thoroughly cleaned, perhaps the mattress, upholstery, floor covering and wall paper changed, does the patient experience relief. Street dust contains horse emanations in sufficient quantity to cause asthma in very sensitive individuals. Patients are sometimes sensitive to organic dusts to which they are exposed by reason of their occupation. A baker may be sensitive to the proteins of wheat or rye flour. Peshkin's¹ patient, a druggist, was sensitive to powdered ipecac which he had handled a great deal during the late influenza epidemic. Walker² cites 2 instances in which jewel polishers became sensitized to the dust of the wood used in the polishing process: in one case orangewood, and boxwood in the other. A tailor may become sensitive to sheep wool. Various face- and tooth-powders may play a part, particularly those in which orris root is an ingredient.

These are some of the more obvious types of dust sensitization, and the dusts are clearly specific. But there are cases in which the connection between dust and asthma is not so evident. Thus, a patient may be sensitive to the dust of a particular dirty cotton mattress. Or the cause may be a particular woolen rug, even though skin tests for sheep-wool protein are negative. Grass rugs and mattings are common offenders. I have knowledge of a case in which a patient was sensitive to the dust arising from a rough-surfaced (oatmeal finish) wall paper.

How are we to discover these cases? In the first place a carefully taken history may give a lead. Should we learn, for example, that a patient has had asthma since living in a particular house or room, that when he leaves that house for a considerable time he is free of trouble, and that he has recurrence of attacks as soon as he returns, it would be obvious that the cause of the asthma lay within those four walls. Such a history is, however, very unusual. More frequently the patient may notice that his attacks are more severe under certain conditions and in certain places. For example, a woman may notice

¹ Jour. Amer. Med. Assoc., 1920, lxxv, 1133.

² Oxford Medicine, 1920, ii, 217.

that, while the dust of sweeping generally gives trouble, the dust in a certain room is especially irritating. Many patients suffer from a multiple sensitization, and the history may be confusing.

It is advisable for the physician to go to the patient's home and investigate conditions. An individual sensitive to feathers is not relieved, although he changes his pillow, because sofa cushions stuffed with feathers have been overlooked. Upholstery, floor coverings, wall paper, hangings should be examined as to their nature and dust content.

Skin tests with dust extracts may be helpful. Several years ago Walker,¹ working with animal hair and dandruff, used extracts prepared by soaking the hair in 14 per cent. alcohol for several days. A drop of the extract is used in the skin test by the cut method. Dust collected from the patient's surroundings may be similarly treated and skin tests made with the extract. Cooke, Clarke,² and others make skin tests by the intradermal injection of filtered dust extracts prepared in a weakly alkaline menstruum with phenol as a preservative. It must be admitted that these methods are crude, perhaps inaccurate, and certainly not as delicate as tests in which pure proteins are used. Thus, it has been my routine procedure to do skin tests with the various feather proteins and with alcoholic extracts of feathers from the patient's pillow. Positive reactions to the pure proteins have always been more marked than those to the alcoholic extracts, and often the latter are only suggestive, or negative. But, as far as the dusts are concerned, it is the only method at present available. It is advisable to do skin tests with the commoner dusts quite as routinely as with the pure proteins of various kinds of feathers and animal hair, and especially in cases with which the various protein tests are negative.

A case in point is the following: Mrs. C. W., a light mulatto aged thirty-eight, was first seen in October, 1920. All her life she has been subject to sneezing attacks coming at intervals of weeks or months the year round, but tending to be more severe

¹ Jour. of Med. Research, 1917, xxv, 497.

² Personal communication.

in the late summer, especially in August and September, 1920. She has always been subject to colds. In November, 1906, after childbirth, she contracted a severe cold, and in that same month experienced her first asthmatic attack. Since that time she has had a more or less constant cough, at times wheezing, especially on exertion, with attacks of paroxysmal dyspnea lasting several hours and relieved by the smoke of burning "asthma powders." The severe attacks come at intervals of one to three weeks, being most frequent in the early spring and late fall, somewhat less in midwinter than in midsummer. They occur usually in the early part of the night, more rarely in the early morning, and occasionally during the day. Dust raised by sweeping causes choking and this is especially noticeable when she sweeps her bed-room. There is no apparent relation to food; there has been no urticaria or drug idiosyncrasy. The patient's grandmother is said to have had asthma.

Physical examination showed a very moderate degree of emphysema, and on "bad days" scattered wheezing râles. Special examination of the nose and throat was negative, a nasal defect having been remedied a year before, without relief. The sputum on culture showed a hemolytic and a non-hemolytic streptococcus, while smears were negative for tubercle bacilli.

The patient was instructed to bring in samples (an ordinary envelope full) of contents of pillow and mattress. These proved to be chicken feathers, and an unusually dusty sample of a cotton mattress which the patient has used for many years. The specimens were each placed in small bottles, covered with 14 per cent. alcohol, and allowed to stand several days, with occasional shaking. Skin tests were then done by the cutaneous (linear cut) method with these extracts, with a series of food and epidermal proteins and with pollen extracts. There was a strongly positive reaction to sunflower and a moderate reaction to short and giant ragweed. The mattress extract test was positive, showing a wheal measuring about 6 mm. in diameter, and a 2-cm. zone of erythema.

The patient was then told to wrap her mattress securely in heavy packing paper and thoroughly clean her bed-room. From

the first there was considerable relief. The severe attacks of dyspnea stopped and the wheezing was much relieved. This so impressed the patient that she promptly bought a new mattress. An autogenous vaccine from the sputum was then given, and potassium iodid and belladonna in small doses. During the following eight months she had but a single attack of dyspnea and occasionally a little wheezing. The cough, while not cleared up, was much improved, and the patient did not report in the spring for pollen treatment as advised. In August she returned with hay-fever and a recurrence of asthma, from which she is now (October) nearly free again.

When such skin tests fail (as they probably often do) to discover an offending dust, other expedients may be tried. Relief is at times obtained in this way: the patient is instructed to change his sleeping room, using a room with bare floor, smooth wall paper, and without upholstered furniture. The mattress should be changed for a thoroughly cleaned one, preferably one not made of horse hair. A silk-floss or cotton pillow should be substituted for feathers. Such measures are at times attended by striking relief. Then by returning piece by piece to the former surroundings the cause of trouble may be discovered. This may be found to be the feather pillow, in spite of the fact that tests with the various feather proteins and an extract of that particular pillow were negative.

It is an interesting fact that bed-room dusts are those most often concerned. It is also a matter of common observation that asthmatic patients date the onset of their trouble to an acute infection of the respiratory tract, and one is led to speculate as to a possible connection between these two. Influenza is often mentioned by patients as the starting-point of their trouble. In others it is a severe bronchitis, and in young individuals whooping-cough. These are all conditions in which there is present a considerable bronchiolitis. Lobar pneumonia is rarely an antecedent of asthma. One must admit the probable tendency to sensitization in these individuals, as evidenced by the commonly positive family history. The thought, however, suggests itself that in these cases the bronchial infection with

resultant irritated and (reasoning by analogy to conditions observed in inflamed intestinal mucosa) more permeable mucosa offers a portal of entry for the sensitizing dose of a foreign protein. Since the patients are usually confined to their bed-rooms during such illnesses bed-room dusts should be the commonest offenders.

The apparent development of sensitization has been observed in chronic respiratory infection as well. Of Luckie's¹ cases, one tuberculous patient developed a cat-hair asthma; another patient bedfast with advanced tuberculosis, after being moved into another room, became suddenly worse, with sneezing, coughing, expectoration, dyspnea, and pulmonary hemorrhage. There was no previous history of asthma or hay-fever. Skin tests gave positive results with the pollen of a trumpet vine in flower just outside the patient's window. Removal of the vine and cleaning the room were followed by relief within twenty-four hours. Such sensitization arising in chronic respiratory infection is significant when one considers the group of cases called asthmatic bronchitis by Walker.² According to him such cases resemble true paroxysmal asthma of long standing in that the latter have become complicated by chronic bronchial infection and its resultant phenomena, such as emphysema. The asthmatic bronchitis cases have a fairly typical history: patients usually past the fourth decade have had for a number of years chronic winter colds; later these patients develop asthmatic symptoms, usually not clearly paroxysmal, though they may be so, and tending to be worse in the winter time. Such patients do not show sensitization.

It is true that there is a large number of such cases. One is, however, not justified in making a diagnosis of non-sensitive asthmatic bronchitis on the history alone, and skin tests should be routinely done. It seems probable that such patients may develop a true sensitization in the course of chronic bronchial infection. I am unable to absolutely prove this statement, and many will say that such a patient who is found later in the

¹ Medical Record, 1920, xcvi, 733.

² Oxford Medicine, London, 1920, ii, 217.

disease to be sensitive was probably sensitive from the beginning, and that his chronic bronchitis was really of an allergic nature. Proof would lie in the observation of non-sensitive individuals with chronic bronchial infection for a period of many years, and there are as yet no records of such cases. The following case, however, from the history strongly suggests the development of sensitization.

A negro forty-two years of age states that fifteen years ago he was discharged from the army because of chronic bronchitis and suspected tuberculosis, with loss of weight and cough of six months' standing. After his discharge he lived an out-of-door life and made a complete recovery. He then entered a clerical occupation in which he has continued to the present. Ten years ago he first had trouble again in the form of a winter cold. This recurred each year with increasing severity, but with no change in the patient's weight and strength. Five years ago he developed the first asthmatic symptoms. These consisted rather in wheezing on exertion and dyspnea in the early hours of the morning than in true paroxysmal attacks. He was free of trouble in the warm season of the year. In the late fall of 1920 the trouble returned and with increased severity, with paroxysmal attacks of marked degree in addition to the wheezing. The paroxysms usually came at night, commonly within an hour after going to bed. With the return of warm weather in 1921 his cough improved and the wheezing became much less, but the paroxysms of dyspnea continued throughout the summer, and were present when he was first seen in August of this year. Physical examination showed a moderate emphysema with no râles in an individual of excellent physique and nutrition. Skin tests showed a 5 mm. wheal to goose feathers, all others being negative. He was told to avoid feather pillows, to have his bed-room thoroughly cleaned, and was given small doses of potassium iodid. He has been free of symptoms for nearly three months.

It is evident that dust sensitization in bronchial asthma is a factor seriously to be considered. In the case with multiple sensitization as shown by the ordinary protein tests the failure

of treatment may be explained by the finding of an etiologic dust. When a patient with allergic asthma, after a period of freedom from symptoms as a result of treatment, suffers a return of trouble the new development of a dust sensitization must be thought of. Finally, we may thus be able to solve some cases that would otherwise be shunted into that rather hopeless group of non-sensitive asthmatic bronchitis.

CONTRIBUTION BY DRS. T. H. WEISENBURG AND C. A. PATTEN

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METHODS OF INVESTIGATION OF PITUITARY DIS- ORDERS, WITH OBSERVATIONS ON SOME OF THE CAUSES AND MANIFESTATIONS OF DYSPITUITARISM

Introduction.—In the study of disorders of the endocrine glands a systematic method of investigation is an absolute necessity, and, recognizing this, we have formulated a method for our own work which we are detailing below. We realize very definitely the limitations which surround an effort of this sort, and yet we believe that no progress can be made by sitting on the scorner's seat and hurling anathema, criticism, and caution at those who honestly attempt to penetrate the uncharted wilderness of endocrine function and disorder. An earnest search for the truth may reveal a fact here and there, which, added to the stock of common knowledge of the subject, furthers scientific pursuit.

The chief causative agents in the production of pituitary dysfunction are probably hereditary and congenital conditions. This is evidenced to a large extent by metabolic changes which mark the individual as an outspoken case. There are, however, other factors which must be considered, and important among these are such diseases as meningitis, syphilis, tuberculosis, the exanthemata, and mechanical disturbances from intracranial lesions. The alterations in structure and function which inevitably follow pathologic conditions are recognized perhaps, but not sufficiently emphasized. For this reason several frank cases of pituitary disease were investigated by us from this standpoint in particular.

The investigation was carried out along the lines of internal medicine, neuropsychiatry, and endocrinology with the hope of establishing a basis for a broad as well as specific interpretation of metabolic disorders. Not only the hypophysis but other endocrine organs were studied simultaneously in order that we might understand a little better, possibly, the influence of pituitary disease upon them. The functional interrelationship of all the structures comprising the ductless gland system is yet to a large extent clouded in a haze of mystery, and requires patient investigation in order that we may arrive at some definite conclusions regarding active therapy or—that which is most hopeful—preventive measures. Whether the pituitary disorder arises as a result of primary defect of the gland, or whether it is secondary to some other condition, such as disease, for instance, or derangement elsewhere in the glandular system, has been our problem in this study, and we are emphasizing more particularly the secondary and end-results of disease processes.

Methods of Examination.—Briefly stated, the examination entails a careful history, an exhaustive physical study, a neurologic and mental examination, and a specific endocrinologic examination. It requires all the aid obtainable from the clinical and laboratory facilities of the modern hospital.

Of great importance in the anamnesis from a general endocrine viewpoint is a painstaking family history, because here we frequently discover many facts which have a definite bearing on the patient's condition. Ordinarily, not having in mind the significance of certain family conditions, the examiner is content with eliciting information concerning disease incidence alone and does not make inquiry into nutritional states and metabolic disorders. Our questionnaire embraces the following:

Family History:

Race.

Longevity.

Geographic environment.

Economic conditions.

Social status.

The occurrence of:

- Goiter,
- Dwarfism.
- Diabetes.
- Giantism,
- Infantilism.

Height.

Weight.

General obesity.

The occurrence of psychoses:

- Manic-depressive,
- Dementia præcox,
- Epileptic psychosis,
- Alcoholic psychosis,
- Involucional melancholia.
- Presenile and senile psychoses.
- Toxic-infectious psychoses.

The occurrence of nervous disease:

- Epilepsy,
- Mental deficiency,
- Convulsions of any nature,
- Bed-wetting,
- Habit spasms and tics,
- Organic lesions,
- Psychopathic taints,
- Psychoneuroses.

The occurrence of gastro-intestinal disorders:

- Constipation,
- Diarrhea (duration and frequency),
- Dysentery.

Cardiovascular disease.

Renal disease.

Syphilis.

Tuberculosis.

Menstrual function:

Age of menses,
Pregnancies,
Miscarriages,
Age of climacterium.

Appearance of secondary sexual characteristics.

Age of puberty.



Fig. 148.—Case I. Hypopituitarism; artificial menopause; probable hypopituitarism; acquired syphilis; epilepsy. A, Front. B, Side. C, Posterior.

The personal history requires definite data concerning many conditions that are not disease entities, as well as diseases themselves, because it not only has a direct significance in the diagnosis of the present case but also teaches us to watch for the appearance of these signs in what may be termed the preventive stage. We inquire concerning:

Character of birth.

Infant feeding.

Age of teething, talking, and walking.

Nutritional state and growth in:

- Infancy,
- Childhood,
- Adolescence,
- Adulthood.

Abrupt or slow changes in growth and nutrition.

School career.

Economic career.

Social status.

Personality and character.

Age of puberty.

Age of development of secondary sexual characteristics.

Sexual abnormalities and irregularities.

Potency and fecundity.

Age of establishment of menses.

Character and frequency of menses.

Pregnancies and miscarriages.

Age of menopause.

Venereal disease incidence.

The exanthemata:

- Duration of disease.

- The severity.

- The complications.

The incidence of acute diseases.

The incidence of chronic conditions.

The tendency to respiratory affections.

The reaction to fever.

The occurrence of gastro-intestinal disorders:

- Diarrhea (frequency and duration).

- Constipation.

- Dysentery.

The various diatheses.

Bed-wetting.

Polyuria.

Appetite for sweets.

Skin diseases (especially eczema).

Incidence of mental and nervous diseases (as in family history), with particular reference to:

Tremors,
Tics,
Convulsions,
Spasms,
Palpitation,
Tachycardia,
Vertigo.

Headache, character, frequency, and usual location.

The condition and development of hair:

Age of beginning shaving,
Frequency of shaving,
Premature graying of hair,
Falling out of the hair.

Anomalies of secretory function.

The physical examination embraces the usual careful investigation for evidences of malfunction and disease. The neurologic examination is made in a routine manner, but with special reference to cranial nerve disturbances and sympathetic and vagotonic manifestations. The mental examination, aside from the detection of psychoses and neuroses, particularly concerns the mental development, intelligence, personality, and abnormalities of character. The detail in these examinations is really very necessary, as a precautionary measure to rule out factors other than endocrine and establish clearly our chain of evidence in the interpretation of all the facts in the final summary of the case.

The Endocrine System.—Osseous system:

Height.

Torso-leg ratio (normally 1 : 2).

Length of arm, forearm, hand, fingers, thigh, leg, and foot.

Prognathism, facial asymmetry, frontal or malar prominence.

Shape of hands and feet.

Circumference of head.

Kyphosis or scoliosis.

Nutritional condition:

Distribution of fat (general or segmental).

Circumference of chest, abdomen, hips, arm, forearm, hand, thigh, leg, and foot.

Skin condition:

Smooth, rough, moist, dry, pigmented, padding of soles and palms, overgrowth of tissue.

Hair distribution:

Face, head, chest, pubes, extremities.

Condition of hair: dry, moist, brittle, gray, falling out, etc.

Outer third of eyebrows scant or full.

Condition of nails:

Ridging.

Presence of lunulæ.

Brittleness.

Thickness.

Condition of teeth:

Crowding.

Spacing.

Character of bicuspid (fang shaped or incisor like).

Color.

Palatal arch:

High or narrow.

Condition of tongue:

Thick, thin, flabby, atrophied, etc.

Character of speech.

Glandular structures:

Thyroid: palpability, enlargements, bruits.

Thymus: outlined by percussion.

Testes: size, development, location, function (presence of active spermatozoa in seminal fluid).

Adrenals: reaction to skin stroking, blood-pressure.

Ovaries: palpability, tenderness, menstrual function.

Pituitary: x-ray examination of sella turcica.

Laboratory procedures:

Complete blood count, observing particularly lymphocytosis and eosinophilia.

Blood chemistry; non-protein nitrogen, urea-nitrogen, sugar, creatin, creatinin, calcium.

Blood Wassermann.

Blood-pressure (taken several days for an average).

Urinalysis: twenty-four-hour specimens — repeated — quantity of output.

Fluid intake for twenty-four hours.

Kidney function (phenolsulphonephthalein).

Spinal fluid—Wassermann, cell count, globulin, colloidal gold.

x-Ray examinations:

Head—for sella turcica, sinuses, and condition of cranial bones.

Chest—for thymus shadows.

Long bones—for epiphyseal conditions.

Fingers—for tufting of distal phalanges.

Sugar tolerance estimation:

(a) Feeding 1.5 gm. glucose (in 3 c.c. of water for each gm.) per kilogram of body weight. Procuring samples of blood before and at three one-hour intervals after ingestion and examining for percentage of sugar.

(b) Feeding glucose, 200 gm. at first and increasing by 50 or 100 gm. at each repetition (at intervals of forty-eight or more hours), and collecting the urine for twenty-four hours in four containers, one for each six hours, then examining for sugar. Normally 150 to 200 gm. is the limit of tolerance, 100 gm. bread and 150 gm. milk are given with the glucose.

(c) Injecting subcutaneously boiled extract of pituitary gland, then repeating tests (a) or (b).

Adrenalin reaction:

Injecting subcutaneously 10 minims of a 1 : 1000 solution of adrenalin and recording the pulse and blood-pressure before and at ten-minute intervals for one hour afterward, and once at the end of two hours. Also observing the reaction to skin stroking, and the development of any constitutional effects, such as tremors, faintness, and effect on the pupils. A leukocyte and differential blood count is made at the end of one-half hour and compared with the previous counts.

Atropin reaction:

Instilling 2 minims of a 2 per cent. solution into the conjunctival sac, recording the pulse and blood-pressure at two fifteen-minute intervals afterward, and comparing them with the observations made immediately before the instillation. Noting the constitutional effects, condition of pupils, vasomotor response, and effect on secretions.

Pilocarpin reaction:

Instilling 1 to 2 minims of a 5 per cent. solution into the conjunctival sac and making the same records and observations as in the atropin test.

Oculocardiac reflex:

Noting change in pulse-rate during thirty seconds of moderate pressure on the eyeballs.

Pituitary test:

Injecting subcutaneously 2 gm. boiled extract of anterior lobe substance and noting the effect on the body temperature (thermic response).

Thyroid test:

Feeding thyroid gland in increasing doses for three to five days, and observing the effect on temperature, pulse-rate, and general condition.

Basal metabolism:

Records made on as many cases as possible, noting the average rating, and any changes after feeding any of the glandular products.

We wish to be understood that the foregoing outline of examinations is not considered infallible, that errors arise in unexpected places, that the whole scheme is elastic and based on methods employed and reported by others in similar endeav-

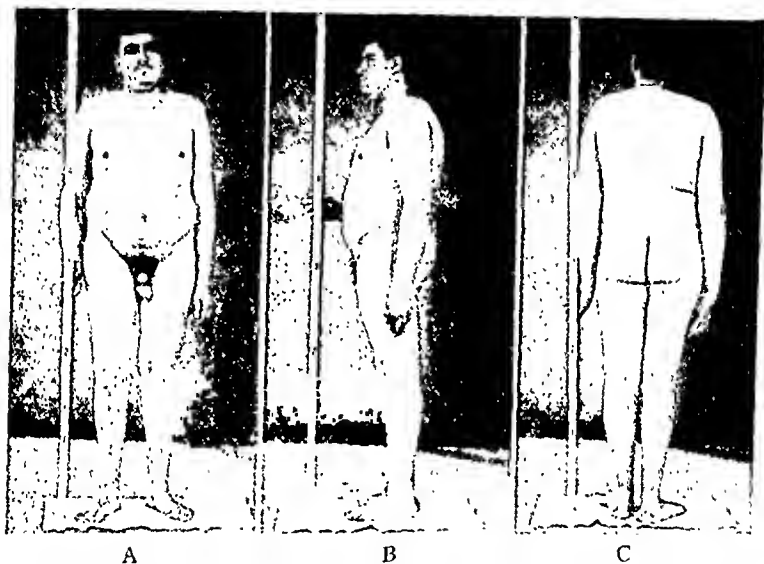


Fig. 149.—Case II. Early hyperpituitarism, but subsequent hypopituitarism; congenital syphilis; internal hydrocephalus; organic nervous disease. A, Front. B, Side. C, Posterior.

ors, as well as our own. While it is advisable to examine every case in the manner detailed above, nevertheless in actual practice, after one is familiar with endocrine cases, some of the tests are omitted because physical examinations clearly indicate the necessity of some of the tests and the futility of others. We would emphasize, however, that conclusions cannot be safely based on the result of one test alone. All the data must be carefully considered, and frequently many tests have to be repeated. The

results in some of the tests may be interpreted in more ways than one, hence the need of following out the whole plan, and building up a conclusion from the entire ensemble of facts.

CASE REPORTS

A few of our cases are abstracted to exemplify types and illustrate the points brought up in the examination methods, and interpretations. For the sake of brevity we are reporting only the final diagnosis in each case and the positive findings regarding pituitary affections. And since the cases are somewhat similar in many of their aspects, they are grouped for discussion, pointing out only individual variations.

Case I.—Hypopituitarism, artificial menopause, probable hypothyroidism, acquired syphilis, epilepsy.

M. F. White, female, aged forty, single.

Family History.—Two maternal uncles were very tall, 6 feet, 3 inches and 6 feet, 4 inches respectively, one was thin and the other stout. One maternal aunt was 4 feet, 1 inch tall. The mother weighed 220 pounds. Two paternal uncles were very short and one aunt was stout; the men were about 4 feet in height, one weighing 100 and the other 150 pounds. One paternal uncle was a bed-wetter all his life. A paternal aunt died in childhood from diabetes and the father had diabetes in 1912. One paternal uncle had four-day attacks of diarrhea at intervals all his life, and 4 paternal uncles suffered from habitual constipation. The father was a bed-wetter until twenty-one years of age and began again at forty.

Personal History.—Normal birth; breast fed; walked at nine months. After the fifth year became dull and indifferent and later violent tempered and fussy. Began growing rapidly at nine. Secondary sexual characteristics appeared, coincident with the change in disposition, at five. No sexual desires until sixteen. Two illegitimate children. Companions chosen from those of low moral standards. Had frequent attacks of sore throat. Bed-wetting occasionally all her life. Oöphorectomy at age of twenty-six, after which no menstrual periods. Convulsive seizures began after the ovaries were removed, with a tendency

to recur near the time of the expected period. Sweats profusely in axillæ and on feet.

Physicial Examination.—Visceral examination negative so far as could be determined. Pupils are irregular, but react well to light.

Endocrine Examination.—Circumference of head, 56.25 cm.; of chest, 122.5 cm.; of abdomen, 125 cm.; of arm, 62 cm.; of thigh, 72.5 cm. Torso-leg ratio 57.5 : 90 cm. Weight 330 pounds. Fat distribution is segmental. Pulse-rate 70; blood-pressure 115/75. Blood count: r. b. c. 4,400,000; w. b. c. 9600; polynuclears 65 per cent., lymphocytes 30 per cent., mononuclears 2 per cent., eosinophils 4 per cent. *x*-Ray examination: The report of *x*-ray examination is from the reading on the plates taken three years ago. The sella is somewhat larger than normal. The floor is intact. The anterior clinoid processes are slightly hypertrophied, the posteriors considerably hypertrophied, meeting the anteriors. A more recent radiograph shows that the sella is larger and shallower than normal, and what remains of it is very thin. There is a bony outgrowth extending downward into the sella from the anterior clinoid process. Sugar tolerance: (a) No glycosuria after ingestion of 800 gm. glucose, (b) blood-sugar before ingestion of 150 gm. glucose, 140 mg. per 100 c.c.; one hour later, 210 mgm.; 2 hours later, 165 mgm. Phenolsulphonephthalein elimination 25 per cent. in two hours. Urinalysis: Specific gravity 1030, otherwise negative. Blood Wassermann 4 plus.

Case II.—Early hyperpituitarism, but subsequent hypopituitarism; congenital syphilis; internal hydrocephalus; organic nervous disease; old interstitial keratitis.

I. E. Male, white; aged sixteen.

Family History.—Father syphilitic (now tabetic) and a first cousin to the mother, who is also luetic. Siblings: 7 (two miscarriages). One sister, age fourteen, 4 feet tall, and weighs 102 pounds; menses began at ten and secondary sexual characteristics appeared at eight or nine. One brother, aged eleven, who developed a deep voice, axillary and pubic hair, and adult-sized genitalia at ten. Sisters, twins, aged nine, began menstru-

ating and developed secondary sexual characteristics between eight and nine.

Personal History.—Normal birth, breast fed, began talking at one year, walking at two years and four months. Had "snuffles" at birth. At six months had otitis media. At three and one-half years, interstitial keratitis. Dull at school. At the age of eleven had diphtheria followed by scarlet fever. At this age began growing rapidly, gaining in height and weight, and to wet the bed. Bed-wetting has continued. Puberty at thirteen. Adult stature at thirteen. Has shaved once. Always good natured, but childish in reactions. Tolerates heat poorly.

Physical and Neurologic Examinations.—Viscera negative. Bilateral deafness—partial. Impairment of vision. Hutchinson teeth. Teeth crowded. Stoop-shouldered. Genitalia normal. Sexually indifferent.

Endocrine Examination.—Height 5 feet, 10 inches. Circumference of head, 53.75 cm.; of chest, 107.5 cm.; of abdomen, 100 cm.; of thighs, 53.75 cm.; of arm, 35 cm.; of forearm, 30 cm.; of hips, 110 cm. Torso-leg ratio 40 : 90 cm. Skin soft to the touch, but doughy on deep palpation. "Milk and roses" complexion. Segmental distribution of fat. Tapering arms and legs (feminine type). Large breasts with large pigmented areolæ about nipples. Blood count: w. b. c. 10,000. Blood-pressure 120/70. Pulse 80. x-Ray examination: Head, marked depressions caused by the convolutions such as is noted in internal hydrocephalus. Sella turcica is deeper than normal. There is some thickening about the posterior wall of the sella. Sugar tolerance: (a) No glycosuria after ingestion of 650 gm. of glucose; (b) blood-sugar before ingestion of 150 gm. of glucose, 134 mgm. per 100 c.c. one hour later, 190 mgm.; two hours later, 154 mgm. Phenolsulphonephthalein elimination in two hours, 20 per cent. (probable error). Blood Wassermann 3 plus.

Case III.—Hypopituitarism; internal hydrocephalus; organic nervous disease. Possible syphilis, latent.

F. F. White, female; aged sixteen.

Family History.—Negative. lues doubtful; possible, as the mother had 14 children, 7 of whom died at birth or in infancy.

Personal History.—Instrumental birth, breast fed, walked at seven months and appeared healthy in every way. At eight months had an infected foot, followed by a period of illness, six weeks in duration, during which she had many convulsions, the head was retracted, and she did not appear to hear or see. The temperature was high and the head was enlarged. She talked at sixteen months, but did not sit up again until four years of age. Vision returned at six years. She never walked again. At five she was a very fat child, unable to use her legs, but could use her hands fairly well. Head measurement at this time 57 cm., and she had spasticity in all extremities, with unsteady movements. There were bilateral ankle-clonus, Babinski, and increased patellar reflexes. She was incontinent. Since then she has had frequent sore throats. Menses established at twelve, but secondary sexual characteristics appeared at seven.

Physical and Neurologic Examination.—Divergent strabismus, nystagmoid movements. Simple atrophy of optic nerves. Teeth crowded. Chronic tonsillar hypertrophy. Scoliosis of spine. Reflexes generally increased. Spasticity in lower extremities with Babinski and clonus present bilaterally.

Endocrine Examination.—Height, 4 feet. Circumference of head, 60 cm.; of chest, 85 cm.; of abdomen, 87.5 cm. Torso-leg ratio 43.75 : 65 cm. Segmental fat distribution. Short arms and legs. Infantile hands and feet. Hypotonicity of joints of arms. Skin dry, smooth, and doughy. Pulse-rate 84. Blood-pressure 110/65. α -Ray examination: Sella is a little deeper than normal, posterior clinoids are thin and stretch practically across the cavity, and are somewhat depressed.

Sugar tolerance: (a) No glycosuria after ingestion of 1000 gm. of glucose; (b) blood-sugar before ingestion of 150 gm. of glucose 104 mgm. per 100 c.c.; one hour later, 106.9 gm.; two hours later, 126 mgm. Blood Wassermann 1 plus. Phenol-sulphonephthalein elimination 40 per cent. in two hours.

Case IV.—Hypopituitarism, acquired syphilis. Psychoneurosis, hysteria.

Z. S. H. White, female, age thirty-five, married.

Family History.—Negative, except that 7 siblings died in early infancy.

Personal History.—Instrumental birth. Very fat baby, breast fed until three years of age. Walked at four and talked at five. Dull in school. Menses began at eleven and hair turned gray in the same year. Married at twenty-five; 9 pregnancies. 5 still-births, and 4 miscarriages. Tremors began in arms five years ago following a blow on the arm and head in a quarrel.



Fig. 150.—Case III. Hypopituitarism; internal hydrocephalus; organic nervous disease; possible syphilis, latent. A, Front. B, Side. C, Posterior.

Physical and Neurologic Examination.—Negative except for functional tremor of left hand and arm and a deformed left foot from an old injury.

Endocrine Examination.—Height, 4 feet. Circumference of head, 55 cm. Length of arm, 27.5 cm.; of forearm, 17.5 cm.; of thigh, 22.5 cm.; of leg, 20 cm. Circumference of chest, 80 cm.; of abdomen, 72.5 cm. Torso-leg ratio 35 : 77.5 cm. Segmental

distribution of fat. Skin dry and rough. Teeth crowded. Pulse-rate 76. Blood-pressure 120/80. Blood count: r. b. c. 4,496,000; w. b. c. 8600; polynuclears 59 per cent., lymphocytes 29 per cent., mononuclears 6 per cent., and eosinophils 6 per cent. *x*-Ray examination: Sella turcica normal in size; hypertrophy of both clinoids; floor intact; clinoids practically meet. Sugar tolerance: (a) No glycosuria after ingestion of 800 gm. of glucose; (b) blood-sugar before ingestion of 150 gm. of glucose 120 mgm. per 100 c.c.; one hour later, 170 mgm.; two hours later, 120 mgm. Blood Wassermann 1 plus. Phenolsulphonephthalein elimination 55 per cent. in two hours.

Case V.—Early hyperpituitarism arrested, now mild hypopituitarism; epilepsy; latent syphilis.

C. T. Male, colored, age fifteen.

Family History.—Negative.

Personal History.—Normal birth, breast fed, growth and development normal until six, at which time a disproportion between the right and left sides was noted. At twelve a Wassermann test revealed a strongly positive reaction. At fourteen began having convulsive seizures epileptic in type, following a year's treatment with arsphenamin.

Physical and Neurologic Examination.—Viscera negative, except for slight hypertrophy of the left ventricle of the heart.

Endocrine Examination.—Height, 5 feet, 3 inches. Circumference of head, 55 cm.; of right arm, 26 cm.; of left, 25 cm.; of right forearm, 16.8 cm.; of left forearm, 15.5 cm.; of chest, 75 cm.; of abdomen, 67.5 cm.; of right thigh, 46.25 cm.; of left, 45 cm. Torso-leg ratio 39.5 : 88 cm. Length of right arm, 32.5 cm.; of left, 30 cm.; of right middle finger, 9.2 cm.; of left, 7.8 cm. Circumference of right hand, 20.75 cm.; of left, 19 cm. Asymmetry of face, the right side being larger. Fat is general in distribution, with slight excess on breasts and a pendulous abdomen. Skin soft and smooth. Upper teeth much spaced and the bicuspid are small and incisor-like. Scoliosis in cervicodorsal region and lordosis in lumbar region. Tilting of the pelvis to the left. Pulse-rate 56. Temperature 97° to 99° F. Blood count: r. b. c. 4,500,000; w. b. c. 13,600; polynuclears 56 per cent., lymphocytes

40 per cent., transitionals 3 per cent., eosinophils 1 per cent. Sugar tolerance: (a) No glycosuria after ingestion of 300 gms. of glucose. Blood Wassermann remains slightly positive. Roentgen examination: Sella turcica normal. Epiphyses open, no tufting of the distal phalanges of the fingers.

Case VI.—Hyperpituitarism (giantism), hypogonadism, epilepsy.

C. R. Male, white, aged twenty-one. Single.

Family History.—Father and mother both very short and slender. Paternal grandfather was a very tall, large man; paternal grandmother very short and slender. A sister is 5 feet, 4 inches tall and very stout. One brother 5 feet, 8 inches tall. Father was fifty-six and mother forty-eight when patient was born.

Personal History.—Normal birth. Bed-wetter until fifteen. Backward in school. Always irritable. Began growing rapidly at fifteen. Mastoid operation at thirteen. Subject to frequent colds. Convulsive seizures began at eighteen, following exposure and prolonged exertion, which recurred frequently for a year and less often during the next year, and since then but one or two. Amputation of left breast at twenty for "tumor."

Physical and Neurologic Examination.—Hearing impaired in left ear. Scar on left chest wall. Poor muscular development. Asthenia. Incapable of much exertion. Viscera negative.

Endocrine Examination.—Height, 6 feet, 3 inches. Torso-leg ratio 46 : 100 cm. Length of arm, 36 cm.; of forearm, 29.5 cm.; of middle finger, 9 cm.; of thigh, 46 cm.; of leg, 47 cm. Circumference of head, 54.5 cm.; of chest, 78 cm.; of abdomen, 64 cm.; of hips, 89.5 cm. Weight, 160 pounds. Little or no hair on face; has shaved but once. No hair on torso. Pubic hair line scant and conforms to feminine type. Marked prominence of malar and maxillary bones. High, narrow palate. Teeth crowded. Skin smooth and soft. Red cheeks. Very little subcutaneous fat. Pulse-rate 60. Temperature 96.6° to 97.4° F. Blood count: w. b. c. 10,640. Polynuclears 72 per cent., lymphocytes 25 per cent., eosinophils 2 per cent., basophils 1 per cent. Blood-pressure 90/55. Sugar tolerance test: Before the

ingestion of glucose 79 mgm. per 100 c.c. of blood; one hour later, 103 mgm.; two hours later, 115 mgm.; three hours later, 87 mgm. Blood Wassermann negative. x-Ray examination: Posterior clinoid process has appearance of being thinned out as from pressure, exerted within the sella. Open type of sella; normal in size. Testes small—about the size of a bean. No spermatozoa in the seminal fluid.



Fig. 151.—Case IV. Hypopituitarism; acquired syphilis; psychoneurosis; hysteria. A, Front. B, Side. C, Posterior.

DISCUSSION

The significance of a careful family history is well brought out in Cases I and II. Endocrine disturbances are very definite. In the first case attention is called to the giantism, dwarfism (*i. e.*, below the average stature), obesity, bed-wetting, diabetes, and gastro-intestinal disorders. In the second case premature development of secondary sexual characteristics, early puberty, and premature physical development are found in the brother and sisters. It is of interest to note that the mental develop-

ment has not kept pace with the precocious physical development. In Case VI there are marked abnormalities of growth in the family, and the boy, now a giant, was born of undersized parents, who were then well along in the declining years of life. A detailed family history was not possible in Cases III and V, but, as noted, it was negative so far as could be ascertained.

Concerning disease processes and the infections, especially syphilis and meningitis, a study of the personal histories affords valuable presumptive evidence. Case II was luetic from birth,

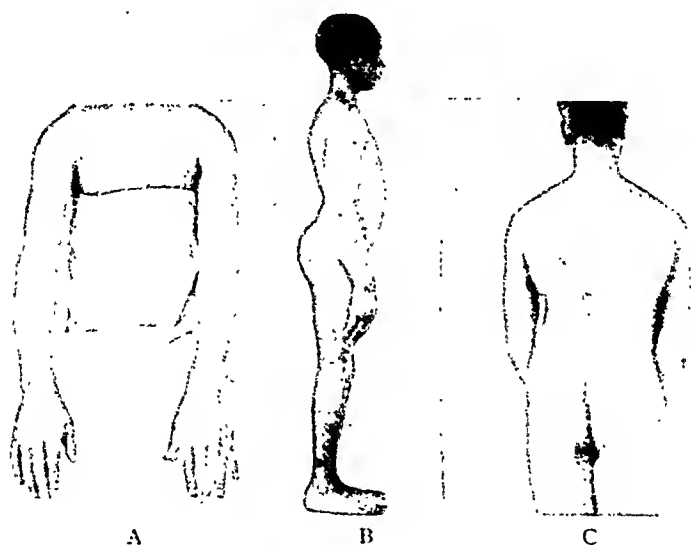


Fig. 152.—Case V. Early hyperpituitarism, arrested; now mild hypopituitarism; epilepsy; latent syphilis; unilateral overgrowth of entire right side. A, Front. B, Side. C, Posterior.

had "snuffles," probably a luetic interstitial keratitis, and developed hydrocephalus. Case III developed meningitis at the age of eight months which resulted in hydrocephalus and lateral sclerosis. In Case IV the instance of the death of 7 brothers and sisters at birth or in infancy is merely suspicious of a possible luetic condition. Case V is also a possible case of congenital lues.

The data furnished in these cases brings us to the question of the influence of syphilis, particularly syphilitic meningitis and endarteritis, on the growth and development of the pituitary gland. From the standpoint of pathology it seems not unreasonable to presume that the gland capsule may have been involved with the basilar meningitis and the growth or expansion of the gland markedly inhibited. Constriction of the infundibulum would cause interference with secretory activity and give rise at least to posterior lobe deficiency. The radiographic studies show an erosion in the sella turcica in Cases III and VI. Assuming that a tense overlying membrane inhibits expansion in the upward direction, then absorption of bone may take place in the floor or at the bases of the clinoid processes. Increased intracranial pressure is found in 2 cases (II and III), the former a luetic and the latter a victim of an infectious meningitis. It is possible that the mechanical factors here have prevented growth and functional activity, producing pituitary deficiency. The anatomic anomaly of clinoid processes practically meeting over the gland must arise from some cause. Speculation might lead us to consider that both basal meningitis and increased intracranial pressure in the formative period of life might result in a maldevelopment of bone and pressure on the enclosed gland. In observing a large number of cranial autopsies on cases other than endocrinous we have rarely found a bridging process such as is revealed in these definite pituitary cases.

The impressions received from the above array of facts and factors lead us to believe that there is at least an opportunity for preventive measures in known cases of pituitary deficiency in early childhood, and possibly will put us on our guard to test out the glandular activity in definite cases of congenital syphilis, or in those with residuals of meningeal involvement from whatever cause.

Considering the physical findings in these cases we note the segmental fat distribution in Cases I, II, III, and IV, and the overdevelopment of extremities in Cases II, V, and VI. The pulse-rate is subnormal in 2 cases and the blood-pressure low in 3. We expected to find a uniformly low pulse-rate and tem-

perature curve in the cases of hypofunction, but when the other findings are considered there seems to be a reason for the variations. The leukocyte count shows an increase, and in the differential a higher percentage of lymphocytes in 5 cases. The interesting feature in Case VI is that his very evident giantism, his pulse-rate, blood-pressure, and leukocyte count conform very

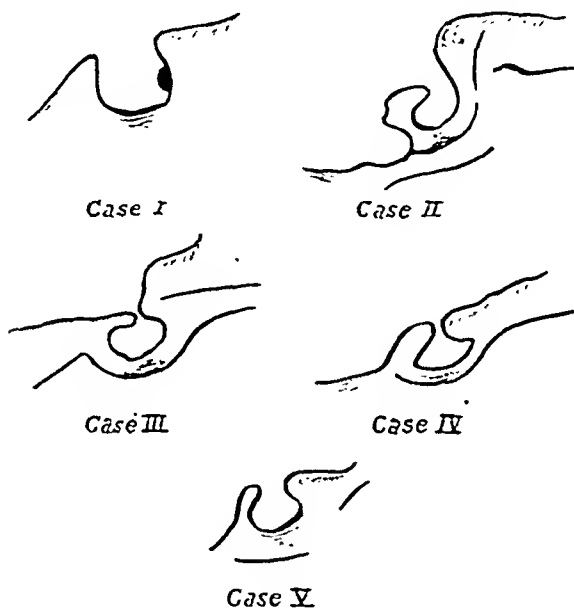


Fig. 153.—Case I. Very large sella; suggestive of tumor. Case II. Unusual outline with hypertrophy of posterior clinoid. Case III. Practical approximation of clinoid processes. Case IV. Small sella with almost approximation of clinoid processes. Case V. Sella turcica practically normal in outline and size.

definitely with the picture we are familiar with in hypofunction. Careful study of other data in the same case might indicate that there is a change taking place from hyper- to hypofunction.

The x-ray studies of the sella turcica show some abnormalities in every case except the fifth. There are variations from normal size to different degrees of enlargement; deepening of the fossæ; erosions of the clinoid processes; hypertrophy of the clinoid

processes; a bridging over of the sella by an overgrowth of the clinoids, and thickening of the walls of the sella.

The sugar tolerance is increased in every case as tested by examination of the urine for sugar except in Case VI, where it was not done. In the normal individual we would expect a glycosuria after the ingestion of 150 to 200 gm. of glucose. By the blood method it is noted that there is a hyperglycemia with a more or less normal sugar curve in 3 cases. In such cases the rôle of the thyroid must be considered. One case has a practically normal blood-sugar content (100 mgm.) on a fasting stomach, but on testing out shows a sugar curve that is still rising at the end of two hours. The sixth case shows a hypoglycemia and a normal curve, but here we have the picture of earlier overactivity of the pituitary, and such a curve might not be unexpected.

The hair distribution in the 2 white males shows a scantiness and configuration that conforms to the opposite sex. The general bodily development in the same cases conforms likewise to the feminine type. The colored boy has a more masculine appearance in many ways, but his hypotrichosis is probably an expression of a racial characteristic.

TREATMENT

There is little that can be said on this phase of the subject. Cases of definite hypopituitarism frequently do not respond in the way we would wish to glandular feeding. Hyperpituitarism that changes after a time to a hypopituitarism theoretically should yield to treatment, but in cases of overactivity, *per se*, there is little that can be done unless it be surgery or x-ray treatment, where tumors are concerned. The main hope lies in preventive measures and early recognition of cases. To attempt to restore to normal an individual who has been undergoing metabolic changes for years is probably a waste of effort. By means of systematic examinations in the incipency of the disorder it is not unreasonable to expect results from appropriate and judicious organotherapy. Without first definitely diagnosing the particular disorder any treatment is to be condemned,

for harm may result. The blind and wholesale feeding of glandular products is pernicious practice and can lead nowhere. Whenever treatment is attempted it should be followed carefully, and governed by laboratory tests as well as clinical conditions. The proper dosage and frequency of administration is likewise material for careful study, and to date there seems to be a wealth of opinions. We believe that small doses given intermittently produces a physiologic stimulus and exercises, as it were, the particular gland in question, giving it a rest for a period, or stimulating it to response by increasing the activity of those structures which bear a reciprocal relationship to it. We are still in the early experimental stage, and our opinions will be subject to radical changes as more facts are proved and our knowledge of function and interrelationship increased. In the cases here reported the results of therapy have been disappointing. Some of them could not be kept under control and others were too long disordered to respond in any way. Others still have not been under observation a sufficient length of time to obtain results. One aim, however, has been to so familiarize ourselves with the frank cases that the less marked may be detected early and a definite line of treatment instituted before it is too late.

SUMMARY

1. Diagnosis of endocrine disorders rests upon a thoroughly careful analysis of each case, employing every facility at our command and eliminating step by step the factors which bear an indirect relationship to the disorder.

2. Systematic methods of investigation are requisite to a full knowledge of the case. Painsstaking in detail, the contributing and causative factors and the end-results should be considered from a broad as well as specific viewpoint.

3. Hypo-activity of the pituitary gland is recognized by the segmental fat distribution, asthenia, loss of sexual power, hypotrichosis, high sugar tolerance, and mental sluggishness.

4. Hyperactivity is demonstrated in overgrowth of bones, particularly of the face and extremities, hypertrichosis, sexual changes, mental alterations, and decreased sugar tolerance.

5. Not all cases fall into a definite classification, and yet it is in these early or indefinite cases that the best results of treatment should be attained.

6. Infectious diseases, particularly syphilis, meningitis, and exanthemata, are more frequently underlying causes than we have perhaps heretofore considered.

7. Convulsive seizures of the epileptic type frequently accompany disorders of the pituitary gland, and deserve a classification apart from the idiopathic epilepsies. They yield in some instances to pituitary feeding.

CLINIC OF DR. C. C. WOLFERTH

UNIVERSITY HOSPITAL

QUINIDIN THERAPY IN HEART DISEASE

TODAY I wish to go over with you the record of a patient with auricular fibrillation who was treated with quinidin sulphate, and then discuss certain features of the action, therapeutic possibilities, and limitations of the drug.

J. C.,¹ white male, age fifty-three, was admitted to the Medical Division July 6, 1921 complaining of palpitation, shortness of breath, and "gas on his stomach."

History of Present Illness.—He had noticed some shortness of breath on exertion and gaseous distention for two or three years, but considered himself well until six months before admission, when he consulted a physician on account of the gas on his stomach and heart-burn. The physician told him his heart was enlarged. About two months later he began to notice palpitation and considerable shortness of breath. Two months after this (two months before admission) he had to give up his work as a blacksmith on account of shortness of breath. In spite of the fact that he stopped work and was carrying out the treatment ordered by his physician, he grew steadily worse up to the time of admission. His feet swelled, he had to sit up in bed to sleep, and he was bothered a great deal by palpitation.

Previous Medical History.—Typhus fever thirty years ago. "Rheumatism" nine years ago, with pain and slight swelling of the joints. The attack incapacitated him for three months. Denies venereal disease.

Family History.—Unimportant.

¹ This case is Case VII of the series reported in "Observations on the Treatment of Auricular Fibrillation by Quinidin Sulphate," in press, Amer. Jour. Med. Sci.

Social History.—Has been a blacksmith for many years and has done a great deal of heavy work. Has not used alcohol or tobacco to excess.

Physical Examination on Admission.—The patient is a man of large frame, good musculature, good nutrition, and looks about the age stated. He is moderately dyspneic as he sits quietly in bed. There is definite cyanosis of lips, finger-tips, and lobes of the ears. Moderate edema of feet and legs.

The heart is greatly enlarged, with a transverse measurement of 19 cm. There is a soft systolic murmur at the apex. The cardiac action is rapid and irregular.

A few crackling râles are heard over the bases of the lungs. The abdomen is somewhat rounded. The liver is enlarged, extending about 5 cm. below the costal border in the mid-clavicular line. A fluid wave is elicited and there is some movable dulness.

Tentative Diagnosis.—Chronic myocardial disease; cardiac decompensation with passive congestion and ascites; auricular fibrillation.

An electrocardiogram taken the next day confirmed the diagnosis of auricular fibrillation. The ventricular rate averaged 123, the Q R S deflections were of low voltage, the T wave iso-electric in Lead II.

He responded well to a régime consisting of rest in bed, limited fluid intake, and digitalis. After a week there was much less shortness of breath, the evidences of passive congestion had disappeared, the ventricular rate was about 70, and the urine, which on admission contained a cloud of albumin and many casts, had almost entirely cleared up. The fibrillation was still present.

The digitalis was discontinued and he received quinidin sulphate 0.2 gram b. d. for one day. No symptoms were noticed, so the following day he was given 0.4 gram t. i. d. This amount was taken for five days without appreciable effect. The dosage was then increased to 0.6 gram t. i. d., and after two days the normal rhythm was restored. The quinidin was then reduced to 0.3 gram t. i. d. and at the same time digitan 0.032 t. i. d.

was given. In spite of the fact that a comparatively large amount of quinidin was being taken, five days later his auricles were again fibrillating. This time three doses of 0.6 gram quinidin sulphate restored the normal rhythm. He remained in the hospital twelve more days without another relapse into fibrillation, and during this time his compensation steadily improved. He was taking 0.2 gram of the quinidin t. i. d. and also small doses of digitalis.

There had been no distinct improvement in his condition immediately after the first interruption of fibrillation except for the prompt disappearance of palpitation. With the resumption of fibrillation, although the ventricular rate was scarcely more rapid than the rate of the normal rhythm preceding it, the palpitation returned, and when fibrillation was again interrupted the palpitation again vanished.

When he was discharged from hospital he was advised to report to the Cardiac Clinic, Out-patient Department. He has been under observation there for over two months. During this time he has received quinidin sulphate 0.3 gram b. d. and digitan 0.065 daily, and the scope of his physical activities gradually increased. He feels well and is now able to take long walks and climb stairs without discomfort. There has been no return of fibrillation.

This patient furnishes one of the best results we have obtained from quinidin therapy. Nevertheless, digitalis played a very important part in the treatment. It is altogether probable that without the use of quinidin the fibrillation would have persisted, but one is not justified in concluding that an equally satisfactory restoration of compensation might not have been obtained by digitalis alone.

Discovery of the Peculiar Effect of Quinidin in Auricular Flutter and Fibrillation.—Quinidin, one of the cinchona alkaloids, chemically isomeric with quinin and resembling it in its physiologic effects, was isolated in 1848. It has been used occasionally in place of quinin in the treatment of malaria. So far as its effect on the heart is concerned, until Frey made known his work in 1918 it had never excited more than perfunc-

tory interest. Santesson had investigated its effects on the frog heart along with those quinin and other cinchona alkaloids in 1893. He concluded that it exerted depressive effects directly on the heart muscle, and in sufficient concentration led to cardiac arrest in diastole. He estimated its toxicity to be about half that of quinin.

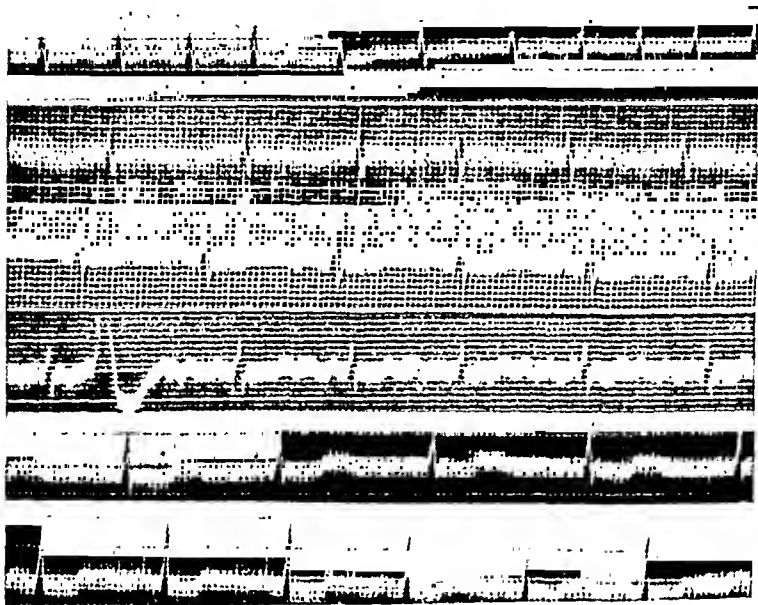


Fig. 154.—Top strip of tracing made July 7, 1921. Auricular fibrillation with ventricular rate of 123. Second strip made July 15th after digitalis treatment. Fibrillation still present, but ventricular rate much slower. Third strip made July 21st after six days' treatment with quinidin sulphate. Normal mechanism restored. Fourth strip made July 26th. Fibrillation again present, but with coarse auricular waves. Fifth strip made July 29th after the second restoration of normal mechanism by quinidin. Cardiac rate, 57. Sixth strip made August 9th. Normal mechanism still present. Marked increase in height of R wave. All tracings, Lead II.

In 1914 Wenckebach reported results that he had observed in restoring normal rhythm in cases of auricular fibrillation following the administration of quinin. Wenckebach's attention had been drawn to this effect of the drug by a patient who

had observed that attacks of irregular heart action from which he suffered were controlled by quinin. Wenckebach recognized that the irregular heart action of this patient was due to auricular fibrillation. Under his observation the normal rhythm was restored a number of times, until finally the drug lost its efficacy for this patient. He then tried the effect of quinin in a number of patients with auricular fibrillation, but was able to restore the normal rhythm in only one other.

Others have found in agreement with Wenckebach that occasionally auricular fibrillation was abolished by quinin, but the proportion of cases favorably influenced was so low that the employment of the drug in clinical medicine for this purpose was scarcely justified. Apparently more favorable results were obtained in treating extrasystolic arrhythmia and paroxysmal tachycardia, but thus far not enough work has been reported to establish its value in these conditions.

The remarkable effect occasionally obtained with quinin led Frey to investigate the properties of the three other well-known cinchona alkaloids, namely, cinchonin, cinchonidin, and quinidin. The first two of these he found of no particular value, but the effects of quinidin were striking. Of the first 22 cases of auricular fibrillation treated with the drug, the normal rhythm was restored in 11. It was also found effective in restoring normal rhythm in auricular flutter. Such results had never been observed previously. Digitalis has very slight if any direct effect in abolishing fibrillation, and the spontaneous restoration of normal rhythm is not common except in paroxysmal fibrillation. Hart states in his book that in his experience but 6 per cent. of cases of fibrillation regain the normal rhythm. Of the last 100 cases studied in this clinic before the use of quinidin, but 5 are known to have regained a normal rhythm, and of these, 2 were cases of paroxysmal fibrillation.

Experimental Studies of the Effect of Quinidin.—At present but little is known regarding the action of quinidin on the heart. In the main, its action is depressant and is probably exerted principally on the heart muscle itself rather than through the cardiac nerves. It appears to cause a distinct depression of

contractility, although it is probably not so potent in this respect as quinin. It also depresses excitability to such an extent that in animal hearts it becomes increasingly difficult and finally impossible to artificially produce extrasystoles or auricular fibrillation. Its effect on the cardiac rate is not so clearly determined. Under some experimental conditions it has been found to slow the rate, but when given to normal persons in therapeutic doses there seems to be no such effect. Changes in conduction under the influence of very large doses may be profound. It is possible to produce complete heart-block and sometimes very rare types of incomplete block in which there may be only one ventricular response to four or even five auricular beats. Schott attempts to explain this unusual disorder of rhythm by assuming that the automaticity of the ventricle is depressed, and instead of taking up an independent rhythm, as it would ordinarily with such a profound disturbance in conduction, it remains dependent for its stimulation on the infrequent excitation waves that manage to traverse the auriculoventricular bundle.

In spite of the remarkable disturbances of conduction observed under experimental conditions, clinical investigators have thus far observed only slight depression of conduction, some maintaining that they have been unable to detect any impairment of this function whatever.

Some very interesting electrocardiographic phenomena have been observed in experimental work, especially by Boden and Neukirch, who found that the P wave might change its relation to the R wave to such an extent that it might follow instead of precede it. Sometimes the P wave dropped out altogether and there was no evidence of any auricular activity whatever. Remarkable changes occurred in the form of the ventricular complex, such as alteration, and finally disappearance of the T wave, decreased height and increased width of the Q R S complex. Decreased height of the T waves has also been observed in clinical studies.

Effectiveness of Quinidin in Restoring Normal Rhythm.—Examination of the reports published up to the present shows

that in about half of the cases of flutter and fibrillation treated a normal rhythm has been restored. The best results were obtained by Jenny, who failed in but 1 out of 18 cases. On the other hand, Klewitz was successful in but 1 out of 13. Such divergent results are doubtless largely explicable on the ground of size of dosage. Klewitz's dosages were small, while those given by Jenny were larger than the average.

In this clinic 12 cases of auricular fibrillation have been treated with quinidin. In 7 the normal rhythm was restored, in 1 fibrillation was converted to flutter, while in 4 the treatment was without effect. In 2 of the 4 failures the treatment was inadequate. One patient left the hospital before the course of treatment was completed; in the other we did not feel justified in giving large doses and risking possible disagreeable effects of quinidin as a cesarean section had been performed only ten days previously and the patient was nursing her baby.

Alterations Produced in Abnormal Cardiac Mechanisms by Quinidin and Comparison with Effects of Digitalis.—A number of observers have noted that the sequence of effects when a patient with fibrillation takes quinidin first tends to be in the direction of the development of auricular flutter and then the restoration of a normal rhythm. Pure flutter with perfectly uniform auricular oscillations in the electrocardiogram is not the rule. This was seen in but one of our patients. But often the auricular waves become larger, more nearly uniform, and the rate may be slowed to that found in flutter. It is probably justifiable to interpret such effects as due to impure flutter, *i. e.*, a transition stage between fibrillation and flutter. This effect of quinidin is seen in the majority of cases treated, whether or not the normal rhythm is eventually restored.

The effect of quinidin on fibrillation apparently tends to bring about a reversal of the sequence of events taking place in the development of fibrillation. According to Lewis there is no essential difference between flutter and fibrillation. Clinically, fibrillation seems to be a more advanced form of arrhythmia than flutter. Flutter is sometimes observed as a transition stage between normal rhythm and fibrillation. Consequently, in the

treatment of fibrillation by quinidin the conversion of the auricular action to flutter is regarded as a step in the direction of normal rhythm.

It is of some interest to contrast the effect of digitalis in these conditions. Digitalis does not convert fibrillation to pure flutter nor even to the transition stage between fibrillation and flutter. It does not convert flutter directly to normal rhythm, as apparently may be done by quinidin, but tends to change it in the opposite direction to fibrillation. Following the development of fibrillation from flutter under the influence of digitalis, a restoration of normal rhythm is much more likely to take place if the digitalis is then discontinued. Digitalis does not materially influence the rate of auricular oscillations in flutter; in fact, the uniform rate of the auricles has always been considered one of the characteristic features of that condition. Quinidin, on the other hand, is capable of markedly slowing the auricular rate in flutter.

Effect of Quinidin on Conduction, as Observed Clinically.—Our observations on the influence of quinidin on conduction through the auriculoventricular bundle tend to substantiate the contention that even in therapeutic doses there is a depression of conductivity. We have observed a slowing of the ventricular rate in auricular fibrillation, and following the restoration of normal rhythm the P-R interval tends to be longer than normal. Even in those patients in whom it does not exceed 0.20 second, it tends to be near that point. But we and also others have observed one effect that is difficult to fit in with the hypothesis that conduction is depressed. After the development of pure or impure auricular flutter the ventricular rate may sometimes be greatly increased by the further administration of quinidin. In our 2 cases that showed this phenomenon the auricular oscillations as noted in the tracings were markedly slowed. While the increase in ventricular rate would seem to point to an increase in conductivity, it is possible that the slower rate of the auricles might in some way favor the transmission of the excitation wave without actual improvement in the function of conductivity.

Effect of Quinidin on Symptoms.—Clinical improvement during treatment by quinidin does not develop as a rule until after the restoration of the normal rhythm. But even then, in the majority of cases, improvement is not rapid. What benefit occurs is probably due to the removal of the mechanical disadvantage to the heart of the disordered rhythm, which in some cases may be very great. Frey states that in his experience the drug exerts no favorable influence on cardiac decompensation. There is no decrease in passive congestion nor does a diuresis develop. On the other hand, there may be unfavorable and even dangerous effects, particularly in cases where the heart is weak.

The drug sometimes acts as a gastric irritant and may cause epigastric distress, nausea, or vomiting. Dizziness, faintness, precordial distress, or increasing dyspnea may be noted. Occasionally alarming symptoms develop, such as extreme tachycardia or even respiratory arrest. Two deaths have been reported in the German literature.

Duration of the Restored Normal Rhythm.—The value of the treatment as a clinical procedure depends not only on the ability to restore normal rhythm but also to retain it after it has been restored. In most patients the factors that led to the production of auricular fibrillation may be assumed to be still active after its interruption by quinidin and may be expected to exert their effects again. Thus in most cases after a longer or shorter time fibrillation usually recurs. It is possible to inhibit this to a certain extent by the procedure recommended by Frey of giving either continuously or intermittently small doses of quinidin. Frey states that in his experience two-thirds of the cases retain a normal rhythm for at least one month. One case has been reported in which the normal rhythm had persisted for nine months and up to the time of the publication had not reverted to fibrillation. In some of our cases the normal rhythm lasted only a few days or weeks, but in 2 it has now lasted over two months. It is in these latter cases that our best therapeutic results have been obtained.

Selection of Patients for Treatment.—The patients in whom

the best results may be expected in the administration of quinidin are those who have had fibrillation for only a short time and whose myocardium is in good condition. Frey has stated that those patients do best whose fibrillation is of "neurogenic" rather than "myogenic" origin. If the fibrillation has persisted for a long time the results of treatment are not nearly so good. In one of our patients who was known to have had fibrillation for at least two years a normal rhythm was obtained, but it lasted only a few days.

It is dangerous to give the drug to patients with decompensation because of the possibility of depressant effects on a heart already so weak as scarcely to be able to sustain the burden of life. But after a measure of compensation has been restored it is permissible to try quinidin therapy.

The age of the patient does not seem to influence the probability of success in treatment, nor does the type of cardiac disease, whether of inflammatory or degenerative origin. The results in cases with or without valvular disease thus far have been about on a par. Patients with decompensation or thyroid disease are said not to be easily influenced, but in 2 cases of thyroid disease and fibrillation treated by us the restoration of normal rhythm was comparatively easy. In one a rapid irregular ventricular rate of 160 was converted to a normal rate and rhythm within twenty-four hours, with an excellent clinical result. In the other the rhythm became normal after six days' treatment.

Details of Treatment.—It is scarcely necessary to say that when the attempt is to be made to restore the normal rhythm in a case of auricular fibrillation the patient should be kept under constant observation and strictly limited as to his physical activities. By preference, he should be in a hospital where observation is likely to be more satisfactory and medical attention can be obtained promptly if needed. It is also a decided advantage to be able to make frequent electrocardiographic examinations. In the present state of our knowledge an attempt to carry out this treatment in an ambulatory patient coming to a physician's office or to an out-patient clinic cannot be too strongly condemned.

Quinidin is almost insoluble, but the sulphate is soluble enough for practical purposes, and is the form of the drug that should be given. It is excreted much more rapidly in the urine than quinidin itself, which is doubtless due to the differences in solubility and, consequently, absorption.

Hypersusceptibility of a small percentage of persons to quinin is well known and a number of deaths have been reported following its use. It is probable that quinidin shares this property. Frey observed 2 cases with alarming symptoms after small doses of quinidin which he interpreted as due to hypersusceptibility. It is therefore advisable to give small preliminary doses of the drug and observe whether or not any unusual symptoms develop. A dosage of 0.2 gram twice in one day is probably enough to bring out the symptoms if there is hypersusceptibility.

The best results in restoring normal rhythm have been obtained by those who have not hesitated to use large doses of the drug. Jenny gave as much as 1 gram three times a day. It is better to start after the preliminary treatment with a dosage of about 0.4 gram t. i. d. and gradually work up cautiously over a period of ten days to the gram doses. If the normal rhythm is restored at any time during this period the large doses of quinidin should, of course, be discontinued immediately. If the first course of treatment is unsuccessful, it may be repeated after a few days' interruption.

The effect of giving digitalis at the same time as quinidin has not been worked out, although the normal rhythm may be restored in some cases while the combination is being taken. Some writers recommend giving the two drugs together. A theoretic objection has been advanced on the ground that since quinidin is supposed to depress the function of stimulus production, if through the combination of the two drugs exerting their effects on conduction complete heart-block should develop, the ventricle might not be able to develop an independent rhythm. But with reasonably close observation and study of cases under treatment it should be possible to prevent so profound a disturbance in conduction as complete heart-block.

During the course of treatment one must be constantly on the watch for possible unfavorable effects of quinidin. The gastric disturbances are probably of no significance and, unless severe, may be disregarded. Such sensations as marked weakness, increased shortness of breath, or precordial distress are danger signals, and the drug should be immediately withdrawn. It has been our practice to stop treatment whenever tinnitus or a feeling of stuffiness in the ears develops or when vertigo becomes pronounced.

In the presence of eye or ear diseases the ordinary rules regarding quinin administration should also apply to quinidin. So far as I am aware, no cases of visual disturbance have been reported after quinidin administration. If any are detected, the drug should, of course, be immediately withdrawn.

What to do if tachycardia develops under treatment is not always easy to decide. If the tachycardia is found to be due to the development of pure or impure auricular flutter and the so-called "deblocking" effect on the transmission of impulses to contraction through the auriculoventricular bundle, experience has shown that the restoration of a normal rhythm is likely to occur if the drug is continued. It is permissible to continue it if there are no clinical evidences of cardiac embarrassment. But if fibrillation is still present and tachycardia develops under treatment, the drug would better be discontinued. This is imperative if subjective symptoms or signs of weakening of the circulation present themselves, otherwise dangerous consequences may ensue.

The Value of Quinidin.—There has not yet been enough work with quinidin reported to estimate what place it will take in the therapy of heart disease. At present the proportion of cases in which it can be used with real advantage to the patient, either with or in place of digitalis, is comparatively small, in our experience not over 25 per cent. Digitalis retains its place as the most important drug in the treatment of auricular fibrillation. It has not yet been demonstrated that those cases most successfully treated with quinidin will not eventually have to rely on digitalis.

But the value of quinidin is not to be measured merely by the practical results obtained by its use in treatment. Its great significance lies in the fact that it has demonstrated the possibility of influencing by drugs aberrant paths of the excitation wave far beyond what previously had been suspected. It has, therefore, opened a new field for research that is very promising. It would appear to be of great value to know just how quinidin is able to remove fibrillation. Already an hypothesis has been advanced by Lewis and his co-workers that it is due to lengthening of the refractory period in heart muscle, hindering the advance of the re-entering excitation wave in the course of its circus movement. On the other hand, depression of conduction through auricular muscle causing retardation of the excitation wave, another of the effects of quinidin, favors the retention of fibrillation since more time is given for the recovery from the refractory period in the path of the re-entering excitation wave. The success or failure of treatment, they believe, depends on whether the refractory period or conduction through the auricle is more affected.

The importance of this hypothesis is self-evident. If it is established, it means that a foundation has been built for the scientific investigation not only of methods of administering quinidin, but of the action of other substances in respect of their possible effects in auricular fibrillation.

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THE DIAGNOSIS AND MEDICAL MANAGEMENT OF DUODENAL ULCERS

I WISH to discuss today the management of duodenal ulcers, and in so doing I will refer in brief abstract to the records of 6 patients who have been studied in this clinic within the past few years; 3 of these were admitted to the private service of Dr. Alfred Stengel and 3 were ward patients. The advantages of including the private patients are that it has been possible to keep in more intimate contact with them throughout the entire course of their disease, and that they have been financially and intellectually capable of more satisfactorily carrying out the prescribed treatment. These are practical factors which must be taken into consideration when deciding upon the method of management.

The failure to appreciate these important factors accounts at least in part for the divergence of recorded opinion, as between the surgeons and the internists, in regard to treatment. Many poor results have undoubtedly occurred because the patients could not afford the time and expense involved in accurately carrying out the medical régime. Such patients have finally come into the hands of the surgeon, and, without consideration of the reason, have been looked upon as medical failures, whereas the lesions were early ones that would have cleared up under medical management had the social status of the patient been different. Such a situation justifies surgical intervention, but does not condemn medical treatment in wholesale fashion. On the other hand, the surgical failures invariably come into the hands of the internists and their mere bulk prejudices the medical

opinion. Neither group of workers sees large numbers of the good results of the other. Also must it be remembered that these two groups of therapists deal in the main with ulcers of different types or in different degrees of development, and that their results can be compared properly only in reference to the specific type of lesion.

In view of these considerations it seems reasonable to believe that as the social status of the patient is given more attention, as final results, both good and bad, are more painstakingly determined and recorded, and particularly as the classification of the lesions is perfected, and results reported in accordance with the particular type of lesion present, will greater uniformity of opinion ensue. A review of the literature on the subject will readily convince one that these factors have not been adequately dealt with, particularly by those surgeons who claim that all duodenal ulcers should be operated upon, and equally by those internists who believe that the great majority, even 90 or more per cent. of those with pyloric obstruction, can be cured by medical means.

Consequently, in order to discuss the management of duodenal ulcers from a broad and at the same time practical point of view, it becomes incumbent upon us first of all to define our clinical classification and to indicate the diagnostic features which characterize the various stages of the disease.

There are apparently those who require only a suggestive history (the Moynihan syndrome of hunger-pains, relief by taking food, and periodicity of attacks) for a diagnosis, but this is not enough, since these symptoms frequently accompany hyperchlorhydria, no matter what its cause, and clear up as the appendix or gall-bladder or other primary cause is adequately dealt with. On the other hand, there are those who insist that only when there is roentgenologic evidence of ulcer is the diagnosis justified. Certainly positive Roentgen data is most convincing, but, even without it, when the symptoms are clear cut and, in addition, there is some definitely localized epigastric soreness, together with the persistent presence of occult blood in the stools (the patient being on a meat-free diet and there being no

evidence of bleeding elsewhere along the gastro-intestinal tract or in the respiratory system), it seems to us that a diagnosis may safely be made. There may or may not be gastric retention. Because of the absence of duodenal cap deformity this type of lesion is commonly referred to as the small non-deforming duodenal ulcer.

When to the characteristic symptoms, melena and localized tenderness, is added Roentgen ray evidence of gastric hyperperistalsis, with early hypermotility and yet some retention, either with or without cap deformity, the diagnosis may all the more confidently be made. If, indeed, the cap deformity is present in all the serial exposures and gall-bladder disease with adhesions is ruled out, the diagnosis is practically certain, and these cases are referred to as having early deforming lesions. The gastric analysis is not of great significance in so far as the degree of total acidity or hydrochloric acid content is concerned, since it has been amply proved in operated cases that normal or subnormal acid figures are present in 15 to 20 per cent.¹ If, however, there is a hyperacidity this is of a certain degree of importance, since 75 per cent. of operated cases show it. Of much greater value in the gastric study is evidence of motor insufficiency or of occult blood in the contents.

If the gastric contents at the end of forty-five to sixty minutes after an Ewald meal equal 200 or more c.c., or fractional removal shows a prolonged high acid curve, and if this evidence of pyloric obstruction is confirmed by the finding in the fasting contents of food from the preceding day or by Roentgen study, together with duodenal cap deformity, whatever the acid figures may be, and whether or not there be melena, a stenosing caloused lesion may be assumed. It is to be understood that in such a case the history is suggestive, and that other causes, such as gall-bladder disease with adhesions, can reasonably be excluded.

There remains but one other type of lesion that must be recognized and separately grouped in so far as treatment is concerned, and that is the deeply penetrating lesion. This may

¹ Eustermann, New York State Jour. Med., 17, 88, 1917.

be suspected by profuse hemorrhage, shown either by the vomiting of large quantities of blood or its passage by rectum. Without hemorrhage this variety of lesion can sometimes be definitely recognized by the roentgenographic plates. It may occur in small and recent lesions or in old and large ones. Also in this group we may include the perforating ulcers, diagnosed by the history of an upper abdominal crisis, with tenderness and rigidity, superimposed upon a history of preceding digestive troubles. Adhesions may accompany any of these lesions except the first one, and need not in themselves alter the treatment.

To summarize, then, we have, from the therapeutic point of view, to consider but four types of duodenal ulcer, as follows:

1. Small non-deforming ulcer, diagnosed by the history, tenderness, and melena, with at times some slight disturbance of gastric motility.

2. Early deforming ulcer with slight gastric retention, diagnosed by the history and the Roentgen-ray findings.

3. Cicatrizing ulcer with stenosis, diagnosed by the history, gastric retention, and the Roentgen-ray findings.

4. Penetrating ulcer, diagnosed by profuse hemorrhage or Roentgen evidence of a deep crater, and perforating ulcer.

GROUP 4

With this simple practical classification in mind we may the more intelligently consider the treatment. In order to further simplify the matter we may immediately dispose of the fourth group by conceding that these cases belong essentially to the surgeon. No one would consider medical treatment for a perforating ulcer, and only the most foolhardy would temporize for long with those who have experienced repeated large hemorrhages or who give a Roentgen picture of deep penetration into the wall of the duodenum. For profuse hemorrhage, however, it may be advisable to treat medically until the patient's general condition warrants operative procedure. In such cases absolute rest in bed is the first essential, and at the same time an ice-bag or, preferably, an ice-coil may be applied to the epigastrium for

the relief of pain and the quieting of gastric peristalsis, hypodermics of morphin may be given for restlessness, and magnesia and calcium carbonate may be given to neutralize the gastric acidity and so prevent its corrosive action on the blood-clot. If in spite of this hemorrhage recurs, or if the patient is markedly exsanguinated, transfusion may be resorted to. The following record will show how we recently handled such a case.

Case I.—W. G., aged forty-nine, male, a lumberman and a resident of South Carolina, was admitted to the private service of Dr. Alfred Stengel at the University Hospital on January 7, 1920, after having experienced a severe hemorrhage from the stomach. His chief complaints were epigastric pain and weakness. He had been in good health until the spring of 1913, when he noticed that any mental worry or stress was associated with a dull burning pain about 3 inches to the right and slightly above the umbilical level. This was always relieved by food or drinking milk. Roentgen study a few months later had showed slight gastric hypermotility. In the fall he had a severe attack of pain after missing his dinner and having some unpleasant business transactions, and subsequently he had numerous recurrences. The following July he was treated by rest and starvation for a short time, this being followed by rather careful dietary management. His attacks then ceased until January 2, 1920, when the old pain returned, again being relieved temporarily by food. The pains grew more and more severe, and on the day before admission, the 6th, while in Philadelphia on business, he was nauseated and vomited a watery fluid. The next day he vomited twice, the contents on the first occasion being reddish and the second time pure red blood with clots. He was then rushed to the hospital, where he was found to be considerably exsanguinated, the skin being pallid and moist, the pulse rapid and irregular, and there being marked restlessness. His stools were bloody, there was much nausea and wrenching, and a point of exquisite tenderness could be demonstrated to the right and above the navel.

He was put to bed, given morphin hypodermically, an ice-coil to the abdomen, and to appease his great thirst a little cracked

ice by mouth. Later bismuth subcarbonate was given every two hours. Horse-serum was administered intravenously several times, and the following day a blood transfusion was done. At this time the red cells numbered 2,500,000 and the hemoglobin was 44 per cent. Three days later the red cells had fallen to 1,360,000 and the hemoglobin to 20 per cent. Small amounts of gelatin were allowed by mouth and water was given second hour in 60 c.c. amounts. Calcined magnesia and bismuth were given to neutralize any acidity that might be present and seemed to relieve the gnawing pain of which the patient frequently complained. Also nitrate of silver in 5-mg. doses was given every two hours. Later a little milk was permitted, and subsequently toast, cooked cereals, oyster broth, ice-cream, custards, puddings, and weak coffee. On the 21st the feces were still black with blood, but the blood count was slightly improved: 1,540,000 red cells and 35 per cent. hemoglobin. On the 26th it was decided to proceed with the operation, and after a second successful transfusion a posterior gastro-enterostomy was quickly performed. Following this there was no further evidence of hemorrhage and the patient rapidly regained his strength. On February 13th his red cells numbered 3,500,000 and the hemoglobin was 52 per cent. He has been seen and heard from several times since leaving the hospital (last time October, 1921) and he has had no further return of his trouble.

While this patient might have been operated upon immediately on admission, such hemorrhages have frequently ceased under medical control, and it seemed only fair to give him the chance of an interval operation. Furthermore, operations done immediately after a large hemorrhage are often disastrous. When the hemorrhage did not promptly cease it then became necessary by means of transfusions to supply as best we could the blood he had lost and so to increase his resistance for the surgical procedure.

GROUP 1

Just as the last group of cases is usually surgical in its indications, our first group may be considered as essentially medical. In the latter are often included that large number of functional

cases with hyperchlorhydria that give no positive evidences of a duodenal lesion, and it is because of this fallacy, we believe, that some medical men are so extremely sanguine about the outcome of simple medical treatment in ulcer cases generally, but we propose to throw out all those cases that do not have in addition to a suggestive history at least melena and local soreness. Some of the cases we include are often cured spontaneously or under some very simple medical régime, but, on the other hand, many are quite resistant to treatment and readily go on to fully developed cicatrizing lesions. Our practice is at once to put all of them to bed, to give a simple carbohydrate diet, moderate doses of alkalies one to two hours after each feeding, and belladonna and bismuth subcarbonate before meals. On this plan of treatment a certain number of them will secure a cessation of symptoms and a disappearance of the soreness and blood in the stools. Such patients after a few weeks may safely be allowed out of bed and gradually returned to their former activities, but for many months, and in some instances years, they should be kept under observation and the diet carefully controlled. Particularly should they avoid acid foods, an excess of meats, stimulants, and condiments.

Others of this group will at first improve, but will again develop their old symptoms as soon as activity is resumed and the diet made more liberal. Still others will not improve at all either symptomatically or as regards the occult blood in the feces or the epigastric tenderness. For these it is necessary to prolong the rest in bed, to simplify and increase the number of feedings; often also, where the acidity is excessive, to increase the alkalies. In patients where symptoms have lasted over a considerable period of time it seems advisable to go immediately to this more strict form of treatment. Particularly is this our custom with ward patients. The following 2 cases will illustrate different methods of managing this type of lesion:

Case II.—J. A. S., male, aged forty-two, was admitted to our wards on March 10, 1921, and gave a three-year history of recurrent attacks of sharp epigastric pain which came on about one and a half hours after eating and was relieved by food. In

the beginning the usual duration of an attack was two weeks, with intervals of one month, but later they had lasted a longer time and had become more severe. There was considerable distention, belching of gas, and some weight lost. Physical examination of the abdomen revealed tenderness on deep pressure just to the right and above the umbilicus. Fractional gastric analysis showed the acid curves to be highest at the end of one and a half hours (free HCl 36, total acidity 68), just when the pain was most severe. The test for occult blood in the stools was positive. The Roentgen examination showed some disturbance of gastric motility, but was otherwise negative, there being no evidence of gastric retention or duodenal cap deformity.

The preliminary clinical examinations having been completed the patient was put on a diet consisting of a 100 c.c. mixture of equal parts of milk and cream hourly throughout the day with sufficient alkalies between feedings to keep the gastric contents neutral in reaction. A week later, the patient still being kept in bed, cereal gruel was substituted for several of the feedings, and a little later a soft-boiled egg and toast. At this time the patient was allowed out of bed a few hours a day, the time up being increased daily, and other simple carbohydrate foods added. A duodenal tube was dropped into the stomach from time to time to insure that the gastric contents were neutral or alkaline.

His symptoms disappeared almost immediately and after the first few days he began to gain weight. On April 13th, slightly more than a month after admission, he was discharged, eating three meals a day and greatly improved in every way.

Case III.—E. C., female, single, of good habits, entered our wards on February 18, 1921, with a complaint of recurrent attacks of burning epigastric pain over a period of thirty-two years, the intervals varying and the pain always being marked when she was hungry and being relieved by taking crackers or soda. A nephropexy was done twenty-five years ago, but did not affect her symptoms. Five years ago a gall-bladder operation was performed, but again there was no relief. For a year she had gastric lavages and during this time she improved some-

what. Three years ago she was treated medically in a hospital for one month without benefit. At times in her attacks she noticed that her stools were quite dark in color. In the last year she had lost 10 pounds in weight. The abdomen showed the scars of her operations and there was a slightly tender spot in the epigastrium. Roentgen study showed slight gastric retention after six hours and moderate early hypermotility. A fractional gastric analysis showed the highest figures at the end of one hour (free HCl 34, total acidity 70) and at the end of two hours the stomach was empty.

The patient did not improve on a simple carbohydrate diet with milk and cream between meals and the use of belladonna and alkalies, and in this instance duodenal feeding was determined upon in order to give complete local rest. It required two days to get the bucket beyond the pylorus, which in itself was suggestive of some spasm in that region, and when it did enter the duodenum she was fluoroscoped to determine its exact location. This being only just beyond the papillary region, she was given a few inches more of the tube and then the feedings by tube were begun. At first she was given 720 c.c. of milk and 3 eggs, peptonized, daily, in eight feedings (740 calories). Almost immediately she began to be more comfortable, and two days later the food was increased so that she got daily 960 c.c. milk, 64 gm. of glucose, and 3 eggs (1120 calories). Water was given at the end of each feeding. After two weeks the patient had lost a little weight, but was quite comfortable. The tube was withdrawn and she was again put on simple frequent feedings of milk, eggs, cereals, and vegetable purees. A few days afterward she was allowed out of bed, and a week later discharged from the hospital on a fairly high calorie diet taken in three meals per day, and quite comfortable.

She has been under the observation of our dispensary since then, but has been able to keep steadily at her work. At the same time she has gained 15 to 20 pounds in weight, now looks very healthy, and only rarely, when indiscrete about her diet, has she had any digestive troubles whatever.

Neither of these patients had positive roentgenologic evidence

of duodenal ulcer, but in both the history was very suggestive and there was a point of localized tenderness in the duodenal area. The first one had occult blood in the feces and the second gave a history of quite dark stools at times. On these grounds we believe that they suffered from non-deforming duodenal ulcers.

The treatment employed with the first patient (Case II) was essentially that described by Sippy, and in our hands this method of management has usually been very effective in this type of lesion. It is based on the idea that the free acid of the gastric contents permeates the exposed surfaces of the ulcer and renders them susceptible to the solvent action of the pepsin ferment, and that therefore the disintegrating properties of the juice may be destroyed by keeping this acid neutralized. This factor being eliminated, it is believed that the ulcers heal in the same way that ulcers on the external surface of the body do and that the passage of non-irritating food is not harmful.

The other patient (Case III) was treated in accordance with a method initiated and championed by Einhorn, its principle being that of complete rest to the affected part. We would point out, however, that when the lesion is a duodenal one it is necessary to allow the tip of the tube to pass well beyond the ampulla of Vater, for otherwise the food will immediately regurgitate into the duodenal cap and be followed by vigorous contractions. This was recently demonstrated in some experiments carried out by Dr. A. S. Doyle, of our x-ray laboratory, and myself. We found that a mixture of milk and barium introduced through the tube while the patient was under the fluoroscope filled the duodenal cap when the tip was in the first or second portions of that organ and that it sometimes occurred when it was in the third portion. It was for this reason that in our patient we took pains to assure ourselves that the tip was as far down as the jejunum. It is probable that this is not necessary when the treatment is being given for a gastric lesion.

These two cases represent the simplest type of duodenal ulcers. Either of the treatments referred to will usually give satisfactory results. When the Sippy type of treatment fails, the symptoms recurring, Einhorn's method of duodenal feeding

should be tried. When both fail, or when the symptoms recur soon afterward with the resumption of a more normal diet and less frequent feedings, we believe surgery is indicated.

GROUP 2

The following cases will represent our second group, the lesion being a more advanced one and demonstrable by roentgenology.

Case IV.—H. S., male, married, and the sole support of his wife and 5 children, came into the hospital on October 7, 1920, giving the following history: Ten years ago he had an attack of stomach trouble which lasted for a month and was characterized by epigastric pain that came on one hour after each meal and was relieved by soda. He had a recurrence five years ago. He was then free of symptoms until three weeks before admission, during which time the pain came on two to three hours after each meal, being very sharp in character and radiating to the right shoulder and back. It often waked him during the night, when he took soda, and was then able to return to sleep. There was some epigastric tenderness. A simple gastric analysis showed a total acidity of 72 at the end of forty-five minutes with a free HCl of 66; there was a decided retention, 235 c.c. of contents being obtained. A fractional test showed prolonged high curves, with a total acidity of 90 and a free HCl of 65 at the end of two and a half hours. The feces revealed no occult blood. The Roentgen study indicated, in addition to the gastric retention, hyperperistalsis with early hypermotility and a constant deformity of the duodenal cap. String test was negative.

On the 19th the Sippy form of treatment, as outlined in Case II, was commenced. Five days later junkets, custards, and ice-cream were added to the milk and cream feedings, and the amounts of the latter were increased. He was free of symptoms from the beginning of this treatment, and his diet was steadily increased and the intervals between feedings prolonged until, finally, on November 20th, he was discharged, getting at that time only three meals a day and a diet which contained 1800 calories.

Case V.—M. L., male, a coal operator, private patient of

Dr. Stengel, was admitted to the hospital October 27, 1917, because of a dull aching pain in the stomach and headache. He had not been well since having typhoid fever five years before, being troubled originally with headache, nervousness, and constipation. During the two years previous to admission he had noticed that he was better when food was in his stomach, and he had developed the habit of keeping something to eat by his bed at night. About three or four hours after each meal he would develop an aching pain in the right epigastrium which could usually be relieved by food or soda. Sometimes in spite of these things the pain would persist with greater or less severity for several days at a time. There would be periods of three or four months when he would have no pain. He often had gaseous and sour eructations. His headaches were relieved by vomiting. His feces were positive for occult blood. Evacuation of the gastric contents forty-five minutes after ingestion showed moderate retention (155 c.c.), and analysis revealed a total acidity of 94 with a free HCl of 35. Roentgen study showed decided gastric retention six hours after the opaque meal, hyperperistalsis and hypermotility, and a constriction in the middle portion of the duodenal cap.

The situation was fully explained to the patient and he was given the choice of a surgical procedure or prolonged medical treatment. Choosing the latter, he was put to bed, given two-hour feedings of milk, eggs, and cereals, alkalies, and daily gastric lavage with 1 : 5000 silver nitrate. On November 7th blood was washed out through the gastric tube. A test-meal on the 13th showed occult blood, a total acidity of 90, free HCl of 59, and still moderate retention (110 c.c.). On the 22d a faint trace of occult blood and acid figures of 82 and 59 were obtained. The following day a duodenal tube was introduced into the stomach, but in spite of hypodermics of atropin it did not enter the duodenum until the third day. He was then given hourly feedings of egg and milk, 120 c.c. at a time, with bismuth and, later, kaolin in the intervals, to affect the duodenal lesion. After a few days the intervals between feedings were increased to two hours and the amounts of food correspondingly increased.

Promptly his tongue cleared, his stomach became more at ease, and at the end of two weeks, as demonstrated by the fluoroscope, the gastric peristalsis was far less active than in the beginning. On the seventeenth day after getting the tube into the duodenum it was removed, but similar feedings by mouth were kept up for a few more days. Then the intervals were increased and other cereals and simple soft carbohydrates were added. Two weeks after the removal of the tube the patient was discharged free of symptoms.

Since then he has been able to keep almost continuously at his work, although he has at times had vague gastric distress, and it has been necessary from time to time to put him on mild gastric sedatives, belladonna and silver nitrate principally. On May 26, 1921 a roentgenologic study showed only a slight gastric residue and peristalsis that was at times quite normal, though the duodenal cap still showed a defect.

These patients presented deforming ulcers that were more advanced than Cases II and III, and it is with reference to such individuals that the question is still unsettled as to whether they should be treated medically or surgically. In some instances it is possible, as it was in Case IV, to explain the situation fully to the patient and to allow him to make the choice, but more often the responsibility rests entirely with the physician. If the patient is intelligent, of good habits, and possessed of sufficient means to allow him, without embarrassment, to be hospitalized for a month or more, and subsequently to limit his activities, take frequent vacations, and always to have his diet carefully controlled, it seems clear that medical treatment is at least safe. If, on the other hand, he is constantly under the strain of supporting a large family by his daily labor and the dieting adds measurably to the stress of his life, it is believed that prompt operation gives him the more satisfactory result. Not all operative results are good, however, and when ineffectual the final result is usually much more crippling than the original ulcer symptoms. It is believed wise, therefore, even in the instance of the ordinary ward patient, to give him at least one thorough trial of medical management. If this fails, operation

should be resorted to. If, for instance, our first patient (Case IV), who had a family of 6 to support by his daily toil, should have a recurrence of symptoms we would advise operation. This advice would be given the other patient (Case V) only if he had numerous recurrences or there was evidence of a progression in his lesion. Minor symptoms in such a patient may well be handled medically.

GROUP 3

Our third group, which is a large one, in our opinion belongs to the surgeon, and it is unnecessary to present any records to identify the cases that belong here. The symptoms are those of pyloric obstruction, pain several hours after meals, usually with vomiting and temporary relief. The pain may be continuous. The vomiting in marked cases may contain food from the day before. Study of the gastric contents shows much residue, ranging from 200 c.c. upward, and the acid figures are frequently high, fractional tests usually showing gradually ascending curves. The Roentgen ray shows a marked residue after six hours and usually marked duodenal deformity. While some men claim that they get results from medical treatment in these cases, some even in 90 per cent., we have obtained no such results, and believe this group should be operated upon promptly.

SURGICAL FAILURES

In addition to the above groups of duodenal ulcers there is one other, which is steadily increasing in size, as more and more ulcer patients are being operated upon, and which inevitably comes into the internist's hands finally. That group is composed of the surgical failures. In some instances the symptoms are due to new ulcers (gastric, duodenal, or jejunal), in others to defective gastro-enterostomies, in still others to adhesions, and perhaps finally to a continuance and progression of the old lesion. Some of these can be benefited by reoperation, but others, in spite of the freeing of adhesions, the repair of the gastro-enterostomy, and what not, continue to have symptoms. These the internist must care for. The following case is illus-

trative of the problem and indicates a method of handling some of these cases:

Case VI.—W. A., male, age thirty-four, had a gastro-enterostomy in February, 1919 for duodenal ulcer, having had typical symptoms for the preceding nine years. He felt well for eight weeks after the operation and then developed pain in the upper abdomen radiating into the cardiac area. In June his abdomen was again opened and adhesions were relieved. After that he had more pain than ever before, it being present constantly except for about an hour after eating or taking soda. The pain became more or less generalized, but was always most marked in the upper quadrant. He had much gas in the stomach and was constantly losing weight.

The physical examination showed him to be rather pallid and somewhat sallow in appearance. There was a slight fulness in the epigastrium and upper abdomen generally and there was some tenderness in this area. Fractional gastric analysis showed the free HCl figures to range from 26 to 41 in two hours and the total acidity from 43 to 71, the curves gradually ascending. There was no occult blood in the fractions or in the feces. Roentgen ray showed the gastro-enterostomy stoma patulous, no gastric residue, and no evidence of ulcer. There was an unfilled area near the pylorus in all the exposures.

On November 13, 1919 he was admitted to Dr. Stengel's private service and a duodenal tube introduced, the location of the tip in the duodenum being determined by the fluoroscope. Through this he was given third hour feedings of peptonized milk and eggs, with subsequently additions of Cream of Wheat gruel and sugar. He stood the feedings well, only rarely having any gastric discomfort. Kaolin in 10-gm. doses in peppermint-water was given by mouth four times a day for its effect on any possible ulcerative lesion. He began to gain weight soon after the duodenal feeding was commenced and in ten days gained 5 pounds. Then the tube was withdrawn and a modified Sippy treatment instituted. Two weeks later he was discharged in good condition and without symptoms. He has had numerous slight recurrences of this trouble during the almost two years

that have now elapsed, but only once has it been necessary to resort to duodenal feeding again for a short time.

GENERAL DISCUSSION

As a result of this discussion it is apparent that we regard only the small non-deforming duodenal ulcers and the early deforming lesions, without evidence of deep penetration into the wall, as amenable to medical treatment. All others, and such of these as fail to respond satisfactorily to a thorough-going medical régime, should be operated upon. It is to be remembered, however, that all ulcers must pass through these early stages in their development, and there is, therefore, with each a time when medical treatment is indicated. Could they all be recognized in these early stages and subjected to intensive medical treatment a far smaller number of them would have to be operated upon. Many patients, however, do not give significant symptoms until the lesions are too far developed for anything short of surgery. This fact emphasizes the desirability of studying exhaustively, including roentgenographic investigation, all patients who present themselves with a history of digestive troubles.

Various clinics throughout this country have developed specific forms of treatment which they apply routinely to these cases, but the fact that these various technics differ in fundamental respects only indicates that none is wholly satisfactory. As will be observed, we have not been in the habit of confining ourselves to any one form of treatment, and have readily shifted even in individual cases from one treatment to another when the results were not satisfactory.

The methods of Einhorn and of Sippy have gained most prominence, the one of rest for the affected part and the other of completely neutralizing the free acidity. Both are undoubtedly of value and in many cases either will accomplish the desired result. Einhorn, in a report upon nine years' experience with his technic,¹ states that all but 4 of 247 gastroduodenal ulcers gave immediate results that were satisfactory, although later

¹ Arch. d. mal de l'app. digestif., 10, 745, 1920.

12 of these had to be operated upon; 15 had relapses from two to five years after the first treatment. He concluded that 95 per cent. of the results were good. Sippy gives equally encouraging reports upon the cases under his management, and believes that even 90 per cent. of the stenotic cases can be cured by his somewhat more elaborate treatment for this type of case. He insists, however, that his treatment even for the milder cases without stenosis must be continued for at least a year. Most other described forms of treatment, while differing in details, have as their basis one or the other of the principles above stated. Some give the local rest by resorting to rectal feeding for four or five days, following this up with liquid and semisolid foods by mouth (milk, soft-boiled eggs, cereals, and later vegetable pureés, rice, custards, marmalades, and jellies). Meats, acid fruits, vinegar, and spices are contraindicated. Many emphasize the value of belladonna for the relief of pylorospasm, though this is perhaps more important in gastric than in duodenal ulcer. Adrenalin has been advocated for its inhibitory effects on peristalsis.¹ The alkalies are almost universally used for at least a reduction in the amount of acidity. Some give duodenal lavage with hot water or soda solution and follow this with 1:20,000 to 1:1000 silver nitrate or 20 per cent. argyrol.

Not infrequently it is intimated that an insufficient number of patients treated medically for ulcer have been followed up over a long period of time to justify the optimistic claims made for this form of therapy. This is to an extent true, since it is very difficult to keep in touch with them, but, on the other hand, every internist is impressed with the large number of definite surgical failures (as Case VI) which he is called upon to treat. In our own wards we see almost as many of the latter cases as we do of primary ulcer. Surely many of these surgical misfortunes could have been avoided by early thorough-going medical study and treatment.

¹ Dorfler, Munch. med. Wch., 68, 246, 1921.

CLINIC OF DR. H. R. M. LANDIS

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OCCULT TUBERCULOSIS

THIS morning I wish to call attention to a form of tuberculosis which is of far more frequent occurrence than is ordinarily thought. It is a type of disease which has been long recognized, but only within the past few years have we given it a name. I refer to what is now known as occult or masked tuberculosis. It is a form of infection of the lungs with the tubercle bacillus which does not manifest itself at all, or only very slightly so, as a respiratory disorder. Its chief characteristics are a state of semi-invalidism accompanied with the evidences of nervous exhaustion, or what is commonly known as neurasthenia.

Weir Mitchell, in his original exposition (*Fat and Blood and How to Make Them*, 1876) of the subject, which he devised for people underweight and suffering from nervous exhaustion, contains a number of case histories which would seem to indicate that the underlying cause in certain of these patients was a tuberculous infection.

For some years I have recognized that there is a type of tuberculosis in which nervous symptoms are the outstanding features. Such cases I have been in the habit of referring to as examples of tuberculous neurasthenia. More often than not they are as well handled, or in severe cases better handled, by the neurologist than the tuberculosis specialist. This is to be ascribed to the fact that rest, seclusion, generous feeding, skilled nursing, and psychotherapy are the chief indications in the way of treatment. And, as a matter of fact, this procedure is what is followed in the ordinary case of pulmonary tuberculosis, with the exception that in the latter group of cases seclusion is not

absolute and the direct application of psychotherapy is not a special feature of the treatment.

Sewall (*Amer. Review of Tuberculosis*, January, 1920) gives an excellent description of this condition:

"These persons are usually not sick with a definite malady, but there is a general functional insufficiency and lack of staying power which can be brought out by submitting them to slight physical strain. They usually suffer from ill-defined misery. Sometimes complaint is made of neuralgic pains in various parts of the body; sometimes of headache and dizziness in the erect posture, and nearly always of undue fatigue at the end of the day.

"Nervousness is a common characteristic. In women the menstrual flow is apt to be scanty or frequently missed. The lungs are rarely suspected, but they give auscultatory signs and an x-ray picture which indicates slight tissue sclerosis involving especially the glands at the hilum and the upper bronchial radiation. The body temperature is usually not elevated, but may rise slightly after exercise. The symptoms may often be traced directly to weakness of the organs of the circulation or to hormonal insufficiency. The medical examiner, according to his individual predilection, would be likely to classify the cases under the title of "neurasthenia" or "hypothyroidism" or other complex of present interest. It seems probable that they form a large proportion of those recruits who were classified by boards of army examiners under the title of "effort syndrome" or "neurocirculatory asthenia."

Sewall lays especial stress on the blood-pressure. In the type of case under discussion the systolic pressure may be normal or indicate a slight hypotension in the recumbent posture, but when the patient assumes the erect position there is a fall in the systolic pressure ranging from 10 to 20 mm. of Hg. Occasionally there is no change in the systolic pressure, but there is an undue rise in the diastolic pressure which reduces the pulse pressure to the neighborhood of 20 mm. Hg. He assumes that a pulse pressure under 30 mm. Hg. is distinct evidence of vasomotor weakness.

Another variation he calls attention to consists of marked rhythmic fluctuations in the height of the systolic pressure, with more or less parallel changes in diastolic pressure.

The following examples may be cited:

Case I.—A woman of thirty-two has been in ill health for the past five years. She has lost about 25 pounds in weight. During this time she has consulted eight physicians and for the past six months has attended the medical dispensary of one of our large hospitals.

Her general condition may be summed up as follows: She has never been too ill to attend to her ordinary household duties. On the other hand, she does this with an effort and at times feels so exhausted that she feels that she must give up. She is also subject to attacks of "nervousness" and is easily upset. Her appetite is poor.

None of the physicians she has consulted has been able to find any evidence of organic trouble. Since attending the dispensary she has been subjected to a variety of laboratory examinations, none of which, however, have thrown any light on her case.

The examination of her lungs is indefinite. There is slight diminution of expansion at the right apex; the percussion rate seems slightly higher in pitch than on the left; expiration is prolonged and slightly blowing in character and the whispered voice is exaggerated. Such findings are not uncommon. They may occur in a lesion just becoming active or they may be the relics of an old healed process. Our determination of whether such a lesion is active or quiescent is based largely on the association of symptoms. If the latter are present, especially slight fever, we assume the process is an active one; if symptoms are wanting we interpret the physical findings as indicating an arrested process. In this case the duration of the ill health and the absence of symptoms point to an old quiescent lesion which, however, is producing sufficient toxins to bring about her condition of nervous exhaustion. As to the roentgenologic findings it may be said that they are of the same indeterminate character as the physical findings. The latter may indicate some

increase in the density of the bronchial tree or show that there is some fibrosis present.

Case II.—A middle-aged woman who for some years has been teaching in a girls' school in addition to caring for her household.

For some years she has always felt badly and "run down" at the end of the school year. A prolonged rest during the summer months, however, always put her in good condition for the following school year. In June, 1921 she felt more tired than she had at any previous time and failed to recuperate during the summer. Her condition this autumn was such that she could not resume her teaching. In addition to marked weakness she was nervous, irritable, suffered from vague pains, and had no appetite. Her pulse-rate was normal and there was no fever. Her blood-pressure was low. The urine showed no abnormal changes. Physical examination revealed slight changes at the right apex. Expansion was slightly diminished, the percussion note impaired, the breathing bronchovesicular in type, and the voice sounds slightly exaggerated. There were no râles.

The roentgenologic examination indicated some fibrosis at the apex. It would seem in this case that there was every indication of an old quiescent lesion which, as the result of overstrain, made itself manifest from time to time, but with rest the nervous phenomena disappeared. Finally, the break became more pronounced and the nervous exhaustion persisted.

Case histories of a similar nature might be multiplied, but these are sufficient to indicate the general character of the disorder. Briefly summarized, these cases of masked or occult tuberculosis all lack nervous energy and are usually depressed. They are also subject to nervousness, complain of neuralgic pains, and tire easily on exertion.

The blood-pressure is usually low, or if normal in the recumbent posture, the systolic pressure falls when they are in the erect posture.

Symptoms referable to the respiratory organs are, as a rule, wanting. They have no fever, cough and expectoration are commonly absent, and both the physical and roentgenologic ex-

amination give a paucity of abnormal findings. In the majority of these cases the source of the trouble is usually wrongly ascribed to some organ other than the lungs.

Incipient tuberculosis, on the under hand, is apt to be characterized by an excess of nervous energy and, as a rule, there is no depression or complaint of neuralgic pain. Slight fever is the rule in incipient tuberculosis and is one of the best means of determining whether slight changes at the apex point to an active or a quiescent lesion.

While the blood-pressure is commonly lower than normal even in the early stages of active tuberculosis, it is not subject to variation as the result of change in posture as is the case in occult tuberculosis. In active incipient tuberculosis respiratory symptoms (cough, expectoration, blood spitting, etc.) and definite physical changes, especially râles, are usually present.

Finally, it must be borne in mind that there are many cases of definite and easily recognized pulmonary tuberculosis in which the nervous phenomena are the outstanding features. Fortunately, in handling these patients the general line of treatment is the same for both.



CONTRIBUTION BY DRS. HERBERT FOX AND
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STERNBERG'S AND HODGKIN'S DISEASES, WITH THE
REPORT OF A CASE

THE subject of Hodgkin's disease, or malignant lymphogranuloma, and of that group of cases to which Sternberg called attention in 1898 still being far from settled, it is profitable to analyze and put on record a case presenting some of the evidences of the first mentioned process, yet with a certain similarity in course and pathologic anatomy to the picture drawn by the above-mentioned author and by him attributed to the action of the tubercle bacillus.

A satisfactory definition of malignant lymphogranuloma has not been written, nor, indeed, can it be maintained that the description given by Sternberg for tuberculosis masquerading under the form of pseudoleukemia is sufficiently definitive to constitute an entity.

The history of Sternberg's disease has been given fully by Sternberg himself in the *Ergebnisse der Allgemeine Pathologie*, 1905, 502; by Karsner (*Archiv. Int. Med.*, 1910, VI, 175); by Baumgarten (*Muench. Med. Woch.*, 1919, 61, 1545), so that it is unnecessary to detail it. One can find an excellent outline of the present conception of malignant granuloma by Longcope in the *Oxford System of Medicine*. The case we report is one in which the main lesions were abdominal. We shall here recite our case and then analyze it from a diagnostic standpoint.

P. P., thirty-five. W. M. S., Greek, was admitted to the University Hospital, service of Dr. Alfred Stengel, for night-sweats, weakness, loss of weight, and swelling of feet. In October, 1919 caught cold, with considerable cough and white frothy sputum.

Some fever, night-sweats, and loss of weight. He had been perfectly well up until this time, but thinks he had some palpable cervical nodes probably two years before this time. Apparently had little medical treatment until July, 1920, when he was told by his doctor that he had trouble with liver and spleen, and very shortly his legs began to swell. This has remained or even increased since. He was in various hospitals from the middle of August until the middle of October, when he was admitted here. Various diagnoses made and variations in the size of the spleen noted. In the summer fingers and toes began to be clubbed. In the fall some pain appeared in right lower abdomen and left hypochondrium, sharp, shooting, and lasting about two minutes; occurred chiefly at night; cough variable, moderate quantities of frothy sputum. Exertion causes dyspnea. Has had occasional gray stools, especially when constipated. No other gastro-intestinal, genito-urinary, or nervous symptoms. History of his stay at the Jewish Hospital indicates that he had a seven-day period of high irregular temperature followed by an irregular practically afebrile period for a similar time, and then nearly two weeks of daily fever with a range of from 5 to 6 degrees. No tubercle bacilli were found in sputum. Wassermann, blood-culture, and urine negative. Blood counts given later. The medical history of patient and family are negative except for the death of mother at sixty-five from cancer. No tuberculosis in family. Social history good. Physical examination 10/14/20 (only positive findings noted): Thin but well-developed man, complexion pasty, movements restricted by large ascites, but respiration not disturbed in rate and rhythm. Mucous membrane of lips and pharynx pale, teeth in generally bad condition, with some pyorrhea and gingivitis. The posterior cervical chain of glands marked on the left; one large gland at angle of left jaw, quite hard, 2 cm.; discrete in chains, soft, not tender. Anterior right cervicals very slightly enlarged, left supraclavicular and axillary regions contain a few small glands. Chest shows poor but equal expansion, this including the diaphragmatic excursion. Percussion note impaired at both apices, especially at second interspace, where mediastinal dulness is

11 cm. wide; third and fourth interspace resonance normal, but below there is dulness marked below sixth rib on both sides, merging into the flanks along a line on the level with the ensiform cartilage. Fremitus is normal above the dulness, absent below. Breath sounds harsh, expiration prolonged, occasional musical or fine crackling râle at apices. Heart apex-beat not visible or palpable, sounds negative. R. B. 4 cm., L. B. 11 cm., R. O. 11 cm., L. O. 15 cm. Abdomen uniformly and smoothly enlarged with tense skin, no enlarged veins; wave and movable dulness present with coronal resonance, especially in epigastrium; liver cannot be outlined; spleen and kidneys not palpable; no masses, tenderness, or hernia. Small soft discrete glands in groins. Edema over the lumbar region, considerable edema of legs to above the knees and some on forearm and hands. Skin of legs shiny, hot, tense, lightly pigmented. Osteo-arthritis of fingers. External genitalia swollen, internal negative. A tentative diagnosis of retroperitoneal or mediastinal new growth involving liver, left lung, and lymph-glands made.

During the course of his stay in the hospital it was noted that the visible membranes became paler and gave the impression of more anemia than his blood showed. Scleræ became subicteroid. For a while, by rest in bed, ascites reduced and the spleen was palpable for several centimeters below ribs; not so the liver. It was discovered that the trachea had been deviated to the right. The pleural fluid was not discovered to be movable and did not increase or decrease materially. The mediastinal mass seemed to increase slightly. Still later in his stay it was possible to measure his spleen (26 cm.); a smooth surface and definite notch. The lymph-nodes did not increase in size, but really decreased under x-ray treatment. A gland was removed about one week after admission and a diagnosis of non-specific lymphoma was made. It was not Hodgkin's, tuberculosis, tumor, syphilis, or leukemia. He, however, was treated on the basis of Hodgkin's, but this seemed to aggravate the process. x-Ray of the chest showed a mediastinal mass which did not change after two weeks of treatment, a finding looked upon by Dr. Pancoast as against the diagnosis of Hodgkin's. x-Ray was.

cytes. Cords and sinuses are not easily distinguished. Venous sinuses are indicated in places and surrounded by fairly prominent endothelial cells. Where sinus can be assumed there is a remnant of the reticulum. The hilum is not present, so its vessels cannot be definitely described. Large ones present show

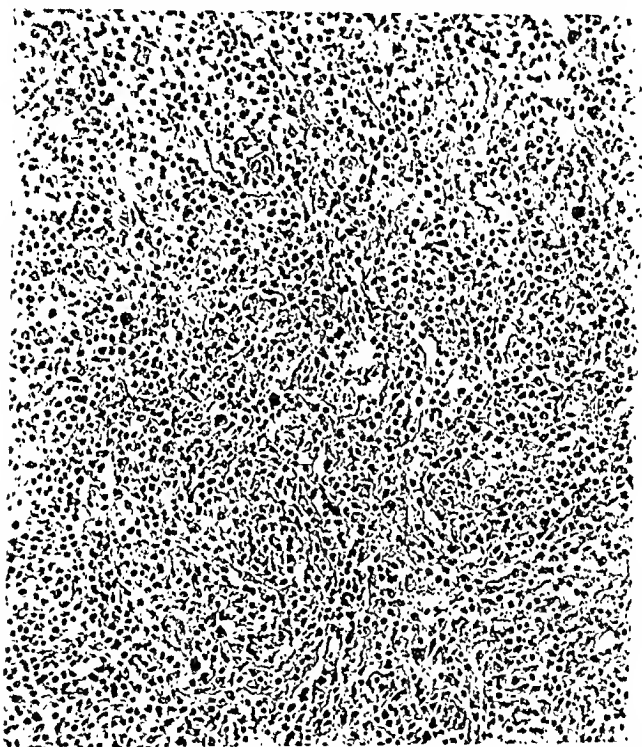


Fig. 155.—516 P. P. First diagnostic adenectomy. Non-specific hyperplasia of lymph-node; prominence of large mononuclears, but not of the Reed type. No eosinophils.

about normal walls. In them and in the venous blood is predominance of mononuclear cells. One large central vein found distended and surrounded by a very delicate fibrocellular wall. The general gland is made up of an irregularly grouped mass of cord and sinus-like arrangements in which the cells are large, small, and middle-sized deeply staining mononuclears with a small amount of cytoplasm. Here and there one will see a large

endothelioid cell apparently in a sinus or on the margin thereof. One seen was distinctly phagocytic of granules and red blood-cells. A few of these cells have two nuclei, some have very distinct vesicular nuclei. In the connective tissue and along cords some of the nuclei are vesicular and elongated. One fair-sized hemorrhage was seen. Pigment here and there, delicate granules, chiefly free. Few plasma cells, no mononuclear cells, polynuclears few and irregularly scattered. No definite granular eosinophils found. A few large cells seen with distinct oxyphilic protoplasm. Some of the large cells mentioned above have a rather deeply stained nucleus and cytoplasm, suggesting myeloid cells more than endothelioid cells, they are not granular, therefore like promyeloids. Giant-cells only of the granular multiple type as mentioned above. In one area there is some advancing fibrosis as indicated by grouping of the connective-tissue nuclei. No necroses or tubercular nodes.

Autopsy performed by Dr. McCutcheon.

Gross Anatomic Diagnosis.

General miliary tuberculosis.

Emaciation.

Jaundice.

Heart: Cloudy swelling.

Hydrothorax.

General lymphoid hyperplasia.

Lungs: Miliary tuberculosis.

Ascites.

Spleen: Splenomegaly undetermined type; probably miliary tuberculosis.

Intestines: Edema.

Liver: Interlobular cirrhosis; miliary tuberculosis; metastatic growths.

Kidneys: Acute tubular nephritis; miliary tuberculosis.

Pancreas:

Prostate:

Testis:

Thyroid gland:

Lymph-node:

Histologic Diagnosis.

Miliary tuberculosis; cloudy swelling; fatty degeneration.

Miliary tubercles and miliary abscesses.

Miliary tuberculosis and granulomata (Sternberg's type).

Miliary tuberculosis and granulomata with fibrosis.

Miliary tuberculosis; fatty degeneration.

Miliary tuberculosis.

Normal.

Normal.

Miliary tubercles (?); parathyroid normal.

Lymphogranuloma (Sternberg's type).

External Examination.—Autopsy held four hours after death. Body of white male aged thirty-five, appearing age stated, measuring 165 cm.; weighing about 125 pounds, of normal frame, emaciated. Skin has icteroid tint of moderate intensity.

Paracentesis wound of lower abdomen. Skin otherwise smooth. Lymph-nodes of neck and inguinal regions are moderately enlarged, hard, discrete. Skull negative. Eyes: Pupils equal, dilated. Scleræ jaundiced. Orifices are negative. Hair distribution normal. Thorax symmetric. Abdomen distended. Genitalia negative. No edema of extremities.

Internal Examination.—*Thorax:* About 500 c.c. of straw-colored fluid in each pleural cavity. No adhesions. Pericardial sac negative. No excess fluid.

Aorta: Is of normal caliber. Intima is smooth, save for vague yellow streaks in abdominal portion.

Heart: 220 gm.; slightly flaccid. Epicardium normal. Myocardium pale, turbid, not fibrosed. Papillary muscles, chordæ tendineæ unaltered. Mural and valvular endocardium smooth, leaflets delicate. Wall of left ventricle, 13; right, 3 mm. Aortic orifice, $7\frac{1}{2}$; mitral, 10; tricuspid, 12; pulmonary, 8 cm.

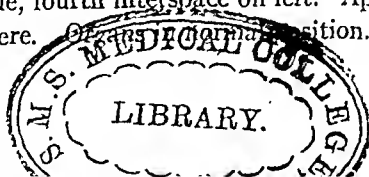
Upper respiratory structures: Trachea and bronchi have pale mucosa. Thyroid gland appears normal. In the superior mediastinum the lymph-nodes are large, up to 2 cm.; firm; pale, and translucent. The glands are discrete.

Peribronchial lymph-nodes: Much enlarged, gray, slightly anthracotic, show miliary tubercles.

Left lung: 850 gm.; third lobe present. Pleura shows many miliary tubercles. Lung is imperfectly collapsed, nowhere is consolidation. Cut surface red in lower lobe, pale in upper; thickly studded everywhere with miliary and small conglomerate tubercles. No larger lesions found. No evidence of chronic tuberculosis.

Right lung: 800 gm.; resembles fellow.

Abdomen: Is distended with clear straw-colored fluid. Peritoneum smooth and glistening. Diaphragm reaches third interspace on right side, fourth interspace on left. Appendix free, no adhesions anywhere.



Spleen: 1370 gm.; 29 x 16 x 7 cm.; firm capsule almost smooth, not adherent to surrounding structures; shape is normal. Cut surface is red, dry. Trabeculae and follicles obscured. In center is a pale yellow, bulging, rather soft mass $2\frac{1}{2}$ cm. in diameter. Similar smaller nodules are found beneath the capsule.

Stomach: Negative.

Intestines: Are markedly edematous.

Bile passages: All the ducts were carefully explored and found normal. In the gastrohepatic omentum is a group of lymph-nodes similar to those described above, in close proximity to the common duct.

Gall-bladder: Is small, contains extremely viscid bile which could be expressed into the duodenum.

Splenic vessels were explored and found free from thrombi.

Liver: 1750 gm.; 33 x 8 x 9 cm.; organ quite firm; surface slightly uneven; capsule transparent. Several more or less projecting yellow nodules are seen; the largest about 3 mm. in diameter. Cut surface red, uneven, lobules distinct. Texture very tough. There are many minute yellowish dots seen, probably miliary tubercles.

Pancreas: Of normal size, consistency, and lobulation. Adjacent to the head and distinct from it are the lymph-nodes described in the gastrohepatic omentum.

Left kidney: 210 gm.; 14 x 6 x 4 cm.; flaccid; capsule strips readily, leaving a smooth mottled surface. Cut surface shows moderate bulging of cortex, which is quite pale with a slightly yellowish tint. Striations are obscured. Glomeruli of normal size. Medulla darker. Striae distinct. Pelvis normal, without increase of fat. Many miliary tubercles are scattered through the renal substance. Cortex, 8; medulla, 20 mm.

Right kidney: 200 gm.; 13 x $6\frac{1}{2}$ x 4 cm.; resembles fellow.

Ureters, urinary bladder, and prostate: Show no changes.

Testicles: Normal.

Adrenals: Of usual size.

Psoas muscle, vertebral column: Appear normal.

Mesenteric nodes: Are moderately enlarged; firm; discrete.

Microscopy.—~~Heart~~ Epicardium is smooth, contains 2

moderate amount of fat. Shows one miliary tubercle. Artery is normal. Endocardium shows no changes. Myocardium presents no interstitial or vascular changes, except for one minute area of fibrous replacement beneath endocardium. A miliary tubercle is shown in one of the sections. Muscle-fibers are of normal size, are irregular in outline, vacuolated, and rarefied. Nuclei usually stain well, but some are obscured. Perinuclear pigment is not prominent.

Lung: Pleura is normal. Interstitial tissue in general shows no changes and supports normal vessels. Alveoli are of usual size. Most of them are empty and show no changes in the walls. A number of miliary consolidations are present, with filling of air spaces and breaking down of walls. Some of these cell collections consist largely of polynuclears, while others show epithelioid and giant-cells, with fibroblasts.

Thyroid gland: Interstitial tissue in general shows no change and vessels are normal. Acini are very variable in size, lining cells appear normal, and colloid is of average quantity. Several miliary areas of cellular infiltration are present with beginning softening. Normal parathyroid tissue is present.

Cervical lymph-node: α -Rayed. Cannot be recognized as such. Consists of a mass of granulation tissue with many capillaries in the cellular areas, considerable blood pigment and small recent hemorrhages, and enclosing in the meshes of the more cellular areas large deeply stained single and multinucleated cells. Plasma cells are numerous. Eosinophils and polynuclears are very scarce.

Node compressing common bile-duct: Adult fibrous tissue capsule. Marginal sinus occupied by lymph-cells, and a coarse fibrosis of the whole gland. Here and there remnants of follicles can be recognized. Most of mass is rather coarse, but loose fibrosis inclosing in an irregular manner small groups of lymph-cells and single or grouped large, deeply stained mononuclears; very deeply staining multinuclears are seen. The reticulum is for the most part active, the larger part being swollen and frequently running strand-wise. Plasma-cells moderate number, eosinophils scarce, mast-cells and polynuclears very scarce, few

deeply staining giant-cells, few necroses, few cellular tubercles such as seen in the lungs. No pigment.

Mediastinal mass: Wide adult fibrous capsule, definite open split below like a marginal sinus. Mass is made up of perhaps 90 per cent. loose but coarse fibrous tissue with swollen connective-tissue nuclei. This surrounds in places more or less

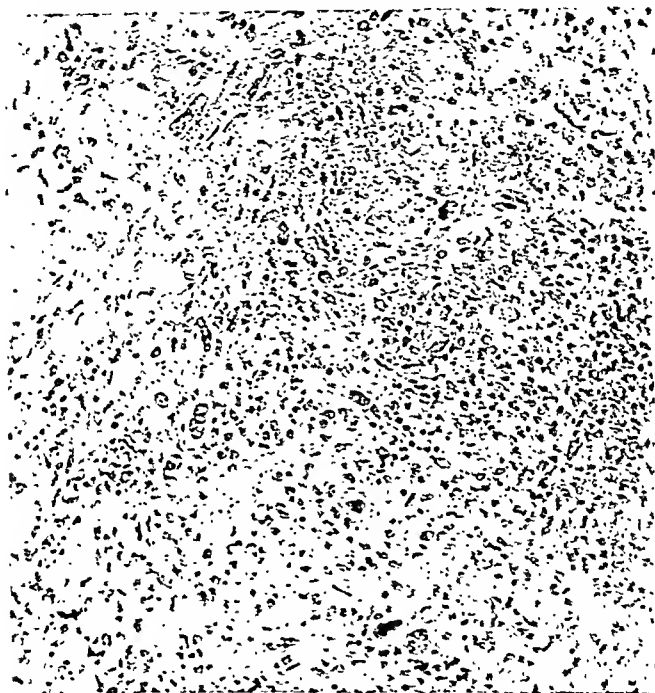


Fig. 156.—590 P. P. B. Section of spleen. Prominent and deeply stained large mononuclears within fibrous tissue. No eosinophils. One tubercle bacillus and a group of Much granules found in this tissue.

definite cellular groups or the fibers pass between the cells. The more cellular areas consist of about equal numbers of lymph-cells and deeply staining nuclei or multinuclei. Plasma-cells are present, polynuclears few, eosinophils practically absent. Few small necroses seen.

Spleen (Fig. 156): Capsule wide, adult, fibrous. Trabeculae

not seen in section. Marginal sinus partly open, partly collapsed. Few indefinite groups which might be follicles and cords. In strands and between cells of cellular groups hemorrhages distributed in strands; coarse brown pigment chiefly extracellular. The more cellular groups consist of about 75 per cent. small mononuclears, 20 per cent. swollen fibroblastic cells, and 5 per cent. of large deeply staining mononuclears and polynuclears. A few neutrophils and plasma-cells are scattered about. Mononuclear eosinophils are exceedingly rare, few necroses, no true tubercles. One abscess-like area such as seen in the lungs.

The caseous mass noted in the spleen consists of an indefinite reticulum and shadows of cells, seeming more like a total necrosis. It is fairly well outlined by a condensation of adult fibers and nuclei. The adjacent spleen diffusely fibrotic, but not so far advanced as the other sections, and with a small number of the coarse deeply staining nuclei.

Liver: Capsule is unaltered. Tissue riddled with miliary tubercles, which obscure the lobular structure. Areas of granulation tissue are present, and fibrous tissue is considerably increased. In granulation areas are found epithelioid cells with extraordinarily large, lobated, deeply stained nuclei.

Pancreas: Interstitial tissue is normal, without changes in vessels or ducts. Islets are of full size. Acini show no changes. A miliary tubercle is present.

Kidney: Capsule is not shown. Extending in from surface are streaks of fibrillar substance which separate and compress the renal structures, and in these areas are found miliary tubercles. Vessels show no changes. Glomeruli in general are unaffected. Tubules have wide lumina, some of which contain hyaline casts. Lining cells are shrunken and vacuolated. Nuclei mostly stain well. Medulla presents no special features.

Prostate: Glandular elements are abundant, but basement membrane is everywhere present. Stroma is normal. There is no cellular infiltration.

Testis: Tunica albuginea unaltered. Seminiferous tubules contain spermatozoa. Interstitial cells appear normal.

Tubercle bacilli can be found in all miliary areas. None

discovered in caseous or caseofibrous parts, but one found in a collection of large deeply stained nuclei. Bodies which might be called Much granules were found by the appropriate stain, lying in caseofibrous and cellular areas. As is usual in this technic, the observer is embarrassed by granular deposits and nuclear fragments. In some seven attempts to find these granules in tuberculous adenitis only twice could one of us (Fox) be satisfied that a picture such as Much gives was faithfully represented, and in four attempts in Hodgkin's disease no success was had.

The history of this case corresponds in a very definite manner with one detailed by Falkenheim (*Zeitsch. f. Klin. Med.*, LV, 130) and with one by Ferrari and Commotti (*Wiener Klin. Rundschau*, 1900, XIV, 1035), but similar histories may be obtained from cases of abdominal Hodgkin's in which no suspicion of tuberculosis exists (Weber, Whittington). In our records we have 2 cases with dominant abdominal involvement, from a total of 20,¹ in which there were vague attacks of pain so localized that in one instance preparation for appendectomy was made. In these cases attacks of pain have been emphasized by Weber (*Practitioner*, 1917, 99, 64) and Whittington (*Quarterly Journal of Med.*, 1916, IX, 83) and others, the case reported by the latter being so severe that operation was planned.

It would seem as though these abdominal pains occur more frequently low in the abdomen, and are in most cases associated with enlargement of the spleen and mesenteric nodes. There may, however, be some relation between the nature of the process and the attacks of pain, for we have seen during the past winter 3 autopsies with enlargement of the spleen, mesenteric and retroperitoneal lymphatic tissue without abdominal crises. Two of these cases were lymphosarcoma, the other an aleukemic leukemia.

It is frequently stated in literature, but perhaps as frequently omitted, that the patient had or had not a tuberculous history. The history of tuberculosis, either personal or familial, is of no significance in the diagnosis of Hodgkin's disease, nor would it

¹ Statements concerning our own cases of lymphogranuloma are based upon cases diagnosed by adenectomy or autopsy.

seem to be in Sternberg's disease. In our records of lymphogranuloma we find but one case with such a story, that in the mother who remained living in fairly good health for several years and not residing with the patient. The histories in recent publications, such as that of Karsner, would indicate the absence of a history of tuberculosis.

In the history of the illness of this case it was noted that regional lymph-nodes were relatively small, firm, and discrete. Such is a common report in the histories of abdominal Hodgkin's. Some of the cases, such as that of Symmers (*Archiv. Int. Med.* 1909, IV, 218), indicate that they were not enlarged at all. The picture as drawn by Sternberg for his tuberculous pseudoleukemia includes cases with small discrete nodes and with large massed or coalescing nodes. It would seem from analysis of the literature that when the primary or dominant early manifestations of the disease in question are abdominal, the cervical, axillary, and inguinal nodes remain considerably less conspicuous than in the form of the disease beginning with lateral cervical tumors. There may be in these cases an involvement of the mediastinal nodes, but it is our impression that the tumors in this location are less apt to complicate abdominal than cervical forms. Lyon (*Amer. Jour. Med. Sci.*, 158, 557), Gibbs (*Med. Clin. North Amer.*, May, 1918, p. 1587), and Weber and Ledingham (*Deutsch. Arch. F. Lin. Med.*, 46, 217) report what seems to be Hodgkin's disease either primary in the chest or with the maximum growth in that location.

The anemia, pasty color of the skin, and the bullous finger-ends with curved nails may suggest a tuberculous basis for the adenopathy. The last conditions may actually be hypertrophic osteo-arthritis. Weber and Ledingham have called attention to this condition, particularly when there has been thoracic involvement. It should be borne in mind that terminal osteo-arthritis is not significant of tuberculosis alone, but implies lack of nutrition at the end of extremities or is due to some toxin; it may be seen in bronchiectasis. This condition was present in our case. The patient had also frequent night-sweats, particularly at the time of his febrile remissions. The examination for

evidence of tuberculosis of the lungs, both by physical diagnosis and by x-ray, failed to reveal signs indicative thereof until quite late in the course when the miliary process was under way. A mediastinal mass of 11 cm. breadth and an effusion extending to the sixth rib on both sides were discovered as early developments.

Lymph-nodes: The history indicates that cervical nodes were slightly enlarged on the left side anteriorly and posteriorly, that there were some above the left clavicle and in the corresponding axilla, and some mild bilateral inguinal adenopathy. There was nothing distinctive about these nodes, but in order to assist in the diagnosis of the splenomegaly one was removed. Its description has already been given, so that it will suffice here to state that a diagnosis of Hodgkin's disease of the Reed type, tuberculosis, leukemia, or syphilis could not be made (Fig. 155). Histologically it does not compare with the picture given by Sternberg or that in Karsner's article. It lacks the areas of necrosis surrounded by deeply staining cells and the strands of endothelioid cells, described as characteristic by the first, and is definitely more fibrotic than the illustration given by the second author. It might possibly be classified by some as the early cellular stage of Hodgkin's disease, but it lacks the definite groups of Reed cells and is much too diffuse in character. In the light of later developments it seems to belong to the lymphogranulomata, but that the section is tuberculosis cannot be maintained. It was unfortunately not put into guinea-pigs because of the size of material, and no thought of tuberculosis had arisen. Ten of our twenty specimens of Reed-Hodgkin's disease have been injected into guinea-pigs and two into rabbits without the discovery of tubercle bacilli in any one diagnosed as being of the Reed type.

The further developments referred to above were as follows: Roentgen treatment of this patient resulted in a complete fibrosis of the lymph-nodes, the usual reaction for lymphogranulomata and different from that shown by the leukemias. This will be the subject of a later paper. Furthermore, at autopsy, as will be seen, the type of granulation tissue in the

spleen, liver, mesenteric and mediastinal nodes was like that seen in the fibrosing stage of Reed-Hodgkin's disease.

The spleen (Fig. 156): Upon admission the presence of ascites prevented a determination of the size and position of this organ, but upon subsidence of the fluid it was discovered to measure 26 cm. in its greatest length of dulness. The gross anatomy of

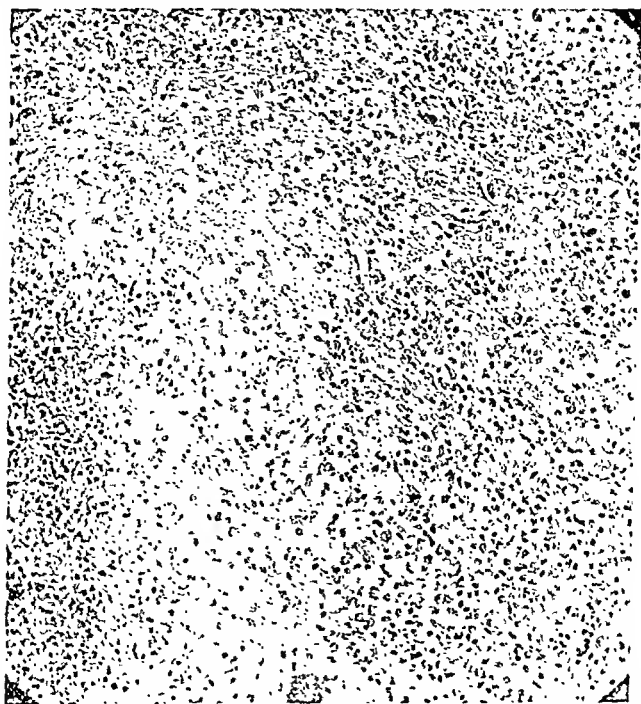


Fig. 157.—216 L. P. Fibrous, necrotizing, and tumor-forming Hodgkin's with uninterrupted course. A stage preceding that to be seen in 581 R. G. Negative for tuberculosis by animal test.

this organ at autopsy presented a picture quite comparable to that given by Sternberg and such as have been seen in many cases of splenic Hodgkin's disease. The miliary tubercles which were present did not seem to alter, or be involved in, the larger nodules of granulation tissue. It is in this organ that the fibrous masses, seen also in the mediastinum and lesser omentum, reach their highest development, and it is in such tissue that Sternberg

and those who agree with him see the peculiar and characteristic cells and architecture. They would see in large cells with deeply staining compound nuclei, strands of pale cells and fibrosis, a kind of granulation tissue different from that of the Reed-Hodgkin's, and Sternberg portrays what he calls Langhans giant-cells surrounding areas of necrosis, the whole being distinctive of his form of pseudoleukemia. In the first place,

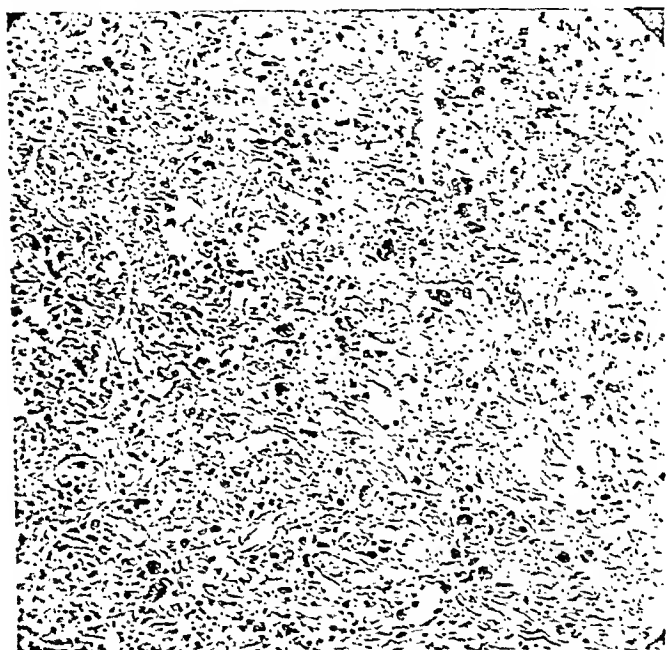


Fig. 158.—581 R. G. Two-year case of tumor-forming fibrous Hodgkin's disease. Note the marked fibrosis inclosing somewhat compressed and deeply stained large cells. Autopsy specimen from mediastinal mass. Compare with P. P. 590, spleen.

necroses with circumferential fibroblastic cells, multinuclear and small mononuclear cells are frequently found in Reed-Hodgkin's. There is no essential difference between the cells in Sternberg's pictures and the multinuclear cells seen in fibrosing lymphogranuloma, and the former are not typical Langhans' giant-cells. In our plates (Figs. 157, 158) can be seen the densely staining

nuclei, single and compound, in cases of very definite fibrosing Hodgkin's in which there was no suspicion of tuberculosis. In some cases of Reed-Hodgkin's, apparently the more active fibrotic variety, connective tissue will entirely squeeze out all the large compound cells, while in other cases, probably slower ones, it will surround and isolate single cells, which, being compressed, take the stain more deeply both in cytoplasm and nucleus. For these reasons we are not inclined to look upon the histologic picture given by Sternberg as indicative of the tuberculous character of this granulation tissue. We would emphasize that in the organs affected by this granulation tissue many small necroses occur.

It is not possible in the histologic preparation to follow clearly the changes produced in the spleen by the alternating enlargements and contractions. It would seem from the observations of Symmers and of Weber that this organ enlarges with the febrile remissions and that this growth is accompanied by focal necrosis. The former writer would see a distinct relation between the necroses and the fever. Such may have been true in our case, but the ascites made it impossible to follow the size at all times. There is nothing to indicate that x-ray had a marked effect upon the spleen; it did not seem to reduce the mediastinal growth.

Liver: This organ was probably increased in size very early in the patient's illness, but seems never to have become very large, being at autopsy only slightly greater than normal in measurements and weight. Anatomically it presents a form of fibrosis with distortion of the parenchyma from irregular connective-tissue overgrowth. Histologically two processes are at hand, a miliary tuberculosis and, at portal spaces, a granulation tissue of coarse fibers, swollen nuclei, polynuclears, small mononuclears, and large, very deeply staining nuclei, single lobed and multiple. This is essentially the lesion seen in the spleen and elsewhere and strictly comparable to that shown in the photographs. No miliary tubercles were seen in this tissue. The fibrosis seems to extend from these areas around lobules, without the development of cirrhosis of a particular type. The connective tissue is fairly cellular.

The participation of the liver in tuberculosis or Reed's lymphogranuloma is in no sense peculiar, according to the literature. The value in this case is as a possible source for dissemination of bacilli, if the original process were tuberculous, just as Reed, Karsner, and Longcope saw invasion of the bloodstream by cells in Reed-Hodgkin's disease. In this case of ours no gross tuberculous center was found, nor were we able to find sufficient invasion or ulceration of parenchyma and vessels to consider seriously the dissemination of bacilli from the liver. Although the early history of the case may point to liver or spleen as the primary focus, it cannot be certainly maintained that the terminal miliary tuberculosis spread from these organs, however much this may seem probable. Moreover, it might be expected that the local granulation tissue would be changed by the outbreak of milia, especially since we were able to find one tubercle bacillus in it (in the spleen), but this seems not to have been the case.

The lymph-node at the hilum of the liver, the growth of which seems responsible for the terminal jaundice by pressure on the hepatic duct, consisted of dense fibrous granulation tissue comparable to that in the spleen and mediastinum; a miliary tubercle was also seen in the sections.

Mediastinum: One of the early discoveries in the case was that of a mediastinal mass, the only effect of which was to produce an effusion on both sides. This part of the body was subjected to x-ray treatment without value, indeed, harm seeming to follow this measure. After an intermission the exposures were resumed, to be followed by another unfavorable reaction on the part of the general condition—fever and depression—and no improvement in the size of the mediastinal mass. The treatment was stopped. In this regard one is reminded of Weber's statement that x-ray is not of service in the severe pyrexial forms of abdominal lymphogranulomatosis. The autopsy notes do not emphasize the mass of discrete, firm, yellow, homogeneous nodes which occupied the superior and posterior mediastinum, with lateral extensions along the bronchi and

attachments to the posterolateral surfaces of the pericardium. This tissue corresponds with that in the spleen.

The blood-picture of this case was that of a mild secondary anemia with leukopenia. The variations in the total leukocyte count do not correspond with any particular feature of the case, but the counts were lower when the general condition was poor. There is no definite course of the differential leukocyte percentages. There is a tendency for the polynuclears to be high during the febrile periods, but their actual number perhaps does not vary, since at this time a leukopenia often existed. It would seem that lymphocyte-producing tissue was inactive at such times and one thinks of the suggested relation of necroses and fever. The clinical notes do not mention variations in size of regional nodes at febrile remissions. The percentages of transitionals, large mononuclears, and eosinophils permit no deductions. The rest of the clinical laboratory tests were either negative or without significance.

The blood counts of abdominal Hodgkin's disease and of Sternberg's granuloma tend to reveal leukopenia or normal limits; exceptionally, high counts are recorded. Usually a relative polynucleosis is mentioned, but at all events no active stimulation of lymphocyte production is evident. In regional Hodgkin's disease, judging by the work of Fabiam, Bunting, Longcope, Steiger, and ourselves, the blood in the well-developed case should show a slight but definite increase in total leukocytes and a relative polynucleosis, with perhaps a small but sustained eosinophilia. The last would seem to occur when necroses are numerous; in this respect our case does not correspond.

A remittent type of fever, usually called after Pel and Ebstein who described it independently in 1887, but first discussed by Murcheson in 1865, is occasionally observed in granulomatosis. Sternberg would put all cases showing this febrile course into his group due to the tubercle bacillus, but it has been reported in cases where tuberculosis seems satisfactorily excluded—McNalty (*Quart. Jour. Med.* 1911, V, 58), Weber (*loc. cit.*), Ruffin (*Amer. Jour. Med. Sci.*, 1906, 131, 587)—unless, of course, all Hodgkin's disease be tuberculous, which is far from proved

today. Our case is a typical chronic relapsing fever of the Pel-Ebstein type, and its course, abdominal lesions, and jaundice resembles that of Weber. It would seem that remittent fever may occur in all forms of Hodgkin's disease according to Longcope, but those who report abdominal types seems to lay stress upon the remittent temperature curve. This case ran a temperature much more irregular and with less systematic periods than those of Weber, of Longcope, of Melland (Edinburgh Med. Jour., 1911, VI, 156), but similar to one of McNalty's cases. The fact that it is relapsing rather than its regularity seems the important thing, especially if it can be shown to be connected with changes in the spleen. Weber's case showed splenic enlargement with each febrile attack. The primary adenectomy in our case showed no necroses in the node, but the tissues at autopsy gave warrant to assume that such focal degenerations had occurred frequently in various places.

A general analysis of the foregoing case reveals the fact that we have encountered an instance of lymphogranuloma which ran a course and presented pathologic anatomy similar to certain cases reported as abdominal Hodgkin's disease and as Sternberg's tuberculous pseudoleukemia. We might add at this point that we agree with Turk and with Symmers that the term "pseudoleukemia" should be dropped as intended to cover a clinical entity, since it is used for forms of disease to be diagnosed correctly as Hodgkin's granuloma and as aleukemic leukemia. Until we shall have reached a more satisfactory understanding of the etiology and basic pathology of these granulomata a correct classification cannot be expected. We can but add our data to those already available in regard to tuberculosis as a cause of Hodgkin's disease. We have complete and satisfactory postmortem records of 7 Reed-Hodgkin's disease without evidence of tuberculosis. We have record of 10 guinea-pig and 2 rabbit inoculations with glands from cellular and fibrosing granulomata, without the development of tuberculosis. The case in question undoubtedly died from miliary tuberculosis, but its source is not evident at autopsy unless it were from the liver or spleen. The course of the case is not sufficiently unlike

others described for Hodgkin's of the abdominal viscera to separate it from them. The intimate association of miliary tuberculosis and the microscopic anatomy as described by Sternberg caused us to study it as belonging to the group detailed by him. It would seem that the gross anatomy of the process is not peculiar and that the form of granulation tissue cannot establish it as tuberculous in nature. At the risk of repetition we would point to the photographs and refer to the pictures given in Sternberg's article. Our pictures contain the same type of deeply staining cell and of connective tissue in the case P. P. However, in the case R. G. (Fig. 158), one of advanced fibrosing Hodgkin's disease without evidence of tuberculosis (animal test twice), the same cells, surrounded and compressed by connective tissue, may be found.

Search for tubercle bacilli was rewarded positively in one section of spleen and one of liver by finding one bacillus. Much granules were searched for and probably found, but we confess considerable skepticism concerning their identity unless they are in such chain form as to give a plausible reason for accepting them; they were not so arranged in these sections.

The tissue changes found at diagnostic adenectomy did not show what later developments revealed, but should perhaps have been "tagged" lymphogranuloma. During the course of treatment with rest, tonics, and x-ray there was perhaps a slight reduction in the size of the primarily discovered nodes, and no new developments, but at no time did they disappear. x-Ray seems to have a decided fibrosing effect upon this nodal enlargement, a fact discovered by a second adenectomy.

The selection of the node for excision is a matter of some importance. If the nodes be growing in masses it is well to choose one within the mass, since this will be more representative of the pathology within the mass than would be a totally separated node. If the nodes be discrete, one of medium consistency, not the softest nor the hardest, should be selected, otherwise the relative proportion of cells and fibrosis will not be found.

Our case showed little effect upon the mediastinal and abdominal masses by the use of x-ray. This cannot be taken as indica-

tive of either Hodgkin's or tuberculosis, but in the light of recent successes in the treatment of tuberculous adenitis by the Roentgen ray and Weber's statement that abdominal lymphogranuloma is little benefited thereby, it suggests that the latter was the principal factor. It might be added that our experience leads us to think that Hodgkin's disease which goes rapidly into fibrosis or is in the fibrosing stage, with the formation of large masses, does poorly under α -ray, whereas the cellular cases are more promising.

It is, of course, out of the question to draw conclusions from the foregoing report, but there are a few points which might be put into concise form. The reported case belongs to the complex group of granulomata by some claimed to be tuberculous in origin, by others as due to the unknown virus of Hodgkin's disease. The patient died of miliary tuberculosis. There was not found a dissemination source for the bacilli, unless it be the hepatic or splenic granulation tissue. The gross and microscopic anatomy does not offer adequate characters to separate Sternberg's tuberculous process and fibrosing lymphogranuloma. The latter in its typical form does not seem to be due to a tubercle bacillus demonstrable by ordinary animal inoculations. However, diagnosis should be assisted whenever practicable by guinea-pig or rabbit inoculation, since there are cases, this one for example, where an exact diagnosis is extremely difficult.

This case showed a refractory attitude to α -ray, as is common in the abdominal and fibrosing variety of granulomata. The rays, however, did cause fibrosis of a cervical lymph-node, and different from that seen in leukemia. It is suggested that the course of treatment in refractory cases be followed by repeated adenectomy.

Paroxysmal pain in the lower abdomen, frequently mentioned in the literature concerning abdominal granulomata, was observed in this case. This class of cases is more often associated with leukopenia than with leukocytosis.

NOTE.—After completing the foregoing report the article by I. Fox (*The Lancet*, July 2, 1921) came to our attention. Case reported by this pathologist is in some ways similar to

our own. The interesting features are the exceedingly marked leukopenia, the involvement of the spleen, liver, and abdominal glands, and the inconspicuousness of the thoracic and cervical nodes. The cause of death in this case seems to have been terminal septicemia with active tuberculosis, not, however, of the generalized miliary type. Unfortunately, neither the English case nor ours can go far to explain the origin of the terminal tuberculosis.

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THE PHYSICAL FINDINGS IN EMPHYSEMA OF THE LUNGS AND MEDIASTINUM

WE have today 3 patients who have been sent to this clinic on account of pulmonary trouble and for examination for tuberculosis. This disease was suspected because of the symptoms of cough, dyspnea, and expectoration in all of them and hemoptysis in 2. They all show bronchitis and well-marked emphysema. None of them presents the ordinary picture of pulmonary tuberculosis. Their ages are forty-three, forty-nine, and fifty-two. Two have worked at dusty occupations, the third is a leather finisher, who states that there is considerable dust produced in his workroom and that he has been exposed to it for twenty-three years.

Pulmonary tuberculosis and generalized emphysema are not commonly associated except in anthracosis or so-called miner's or stone-cutter's asthma. It seems not uncommon to have tuberculosis develop late in life in these cases of anthracosis, consequently, in these patients here present we must look for tuberculosis even though they are obvious examples of non-tuberculous pulmonary disease. In chronic fibroid tuberculosis there is eventually associated an emphysema of the less fibroid portions of the lung. This gives rise to symptoms of emphysema, but not to the usual appearance of an emphysematous chest. The lung is so limited by fibrous bands that it cannot as a whole expand as in generalized emphysema. The chest is shrunk instead of barrel shaped and the cardiac and hepatic areas of dulness are not obliterated.

The presence of bronchitis, asthma, and emphysema complicate the signs to such a degree that it is impossible to recognize

the presence of pulmonary tuberculosis by physical examination. In lungs which are normal except for a localized tuberculous infiltration the signs of the disease are plainly elicited and the diseased area can be accurately differentiated from the healthy portions, but when pulmonary disease of a non-tuberculous nature is also present we cannot determine by signs the limits of the tuberculous process.

The examination of sputum in serial specimens constitutes the most important point in the diagnosis of tuberculosis when there is a marked bronchitis and particularly when emphysema is present. Sputum specimens which are mucoid in character may be repeatedly negative, but when there is a purulent bronchitis there is more apt to be a release of tubercle bacilli into the sputum.

We have had a series of sputum examinations on each case, and in each one the results have been negative.

These patients show, in different degrees, the same signs—distention of the chest, poor expansion, lack of outward movement of the rib margins on inspiration (to which attention has been directed by the careful observations of Hoover), indeed, in 2 patients the ribs draw inward on inspiration with a sharp outward snapping just at the beginning of expiration. There is evident dyspnea at rest and some cyanosis in 2 of the patients. The third is very short of breath on exertion. On percussion we note the classical box-like note, the absence of cardiac and hepatic dulness in two of them, and the extremely low position of the limit of pulmonary resonance at the back, with limited respiratory motion of this line, showing the permanent low position and limited range of motion of the diaphragm.

There are certain signs which I have observed in emphysema of this type which show up very well today in one of these men. You will note on percussion of the back that there is an area of dulness extending a hand's breadth up from the probably lower limit of the lung. Breath sounds are practically absent on this area, voice transmission is feeble. Is there an effusion at the right base? Probably not, as the voice, if transmitted as well through an effusion as it is here, would have an egophonic char-

acter, and the breath sounds in this case, though distant and scarcely heard, are not tubular. There is a slight variation of the margin of the dull area on respiration.

We will now ask the patient to take two or three very deep breaths—now cough—cough again—now another deep breath.

Percussion over the right base now gives a hyperresonant note, breathing is now superficial instead of distant. What has happened to the dulness?

These emphysematous individuals may show great variation in the percussion note. If a dull area is found forcible breathing and coughing may promptly transform the dulness into hyperresonance, and change the lung from a condition of localized collapse to one of distention.

This shows very well the difficulty of depending on physical signs in advanced emphysema. This change in signs on a given area is characteristic of the condition. It is not always present, but may be very striking in any of these patients, and may be very puzzling—not so much possibly in the diagnosis of tuberculosis as in suspected pneumonia when bronchitis is active in an emphysematous patient, or in the diagnosis of fluid in the chest after the almost inevitable break in cardiac compensation has occurred.

Inflammatory pleural exudates tend to take unusual positions in the presence of marked emphysema. Instead of gravitating to the base or the posterior and lateral sulcus they show a tendency to seek the edges of the lung or the interlobar fissures or to lie in vertical columns. If effusion is massive, and the emphysematous lung defies pressure and remains distended under tension, as it may with severe obstructive bronchitis, it gives all the physical signs of an open pneumothorax or enormous cavity.

This x-ray plate shows the chest of a patient in whom these signs persisted for three weeks until the chest was opened and thoroughly drained. You will note that there is a large effusion on the right, no cardiac displacement, as adhesions are dense along the mediastinum, and a clear upper portion of the chest. There was absolute immobility of the right chest, and the signs over the upper portion were those of a pneumothorax. Had this

lung not been emphysematous to an extreme degree there would have been collapse and compression of the lung, with corresponding physical findings.

In emphysema the air vesicles are distended. In chronic emphysema their walls are stretched, torn and atrophied, and incapable of restoration. Even in so-called acute emphysema restoration of elasticity probably takes place to only a very limited degree.

Atrophy and distention with loss of elasticity proceed together. Distention destroys the capillary supply of the tissues and the loss of effective blood distribution results in atrophy. The capillary destruction would seem, at first thought, to cause an immediate pulmonary artery stasis with right heart embarrassment, but it is held on good authority that new connections are promptly established between larger branches of the pulmonary artery and pulmonary veins, so that excessive increase of pulmonary arterial pressure is avoided, though proper aëration of the blood is interfered with. With weakening of the vesicular walls distention will occur as soon as strain is excessive. Cough is the common cause of sudden strain. Bronchitis is a common cause of cough and of emphysema. Severe bronchitis attacking the fine bronchioles causes vesicular atrophy by interference with the blood-vessels and causes distention by bronchial blockage and induced cough. Paroxysms of bronchial asthma, if of a purely spasmodic nature, may occur frequently for long periods of time without setting up a serious emphysema; on the other hand, a severe infective bronchiolitis may cause a severe emphysema in a remarkably short space of time.

Hardened specimens of emphysematous lung do not give a true picture. Under this microscope you will see an unusual specimen of a lobar pneumonia supervening on an acute emphysema in the stage of recovery from influenza pneumonia. The right upper and middle lobe were involved in the lobar pneumonia. They occupied almost the whole of the right chest, the lower lobe being insignificant in a collapsed state. The fibrous and cellular exudate of the lobar pneumonic process made a cast of the distended lung which shows beautifully the enormously

distended vesicles bursting into each other. Compare this specimen with a section of a collapsed lower lobe and bear these two pictures in mind in considering the physical signs which we found in our patient. The whole lung in its distended state would be much larger than its chest. It is obviously impossible for the whole lung to be fully distended at one time. There may be a partial distention of the whole lung, giving a uniformity of physical signs, or there may be a well-distended portion occupying more than its share of the chest, with a relatively collapsed condition of the remainder of the lung, giving very different physical signs. This irregularity in aëration is more apt to be well marked when severe bronchitis is present. Equalization of pressure in different portions of the lung may take place slowly while the chest is immobile between respiratory efforts, the air leaving the overdistended portions and entering the relatively collapsed tissue. Thus râles may be heard while the chest wall and diaphragm are held motionless, and the shifting of portions of the lung may cause blurring of the lung markings on x-ray plates in some areas, while in other parts the detail is clear.

Different types of emphysema are described under varying names. The common type of chronic emphysema is termed "large-lunged emphysema" or "hypertrophic emphysema"; the latter term is a misnomer and in no way descriptive of the condition. Emphysema is essentially an atrophic condition.

Senile emphysema or, better, senile atrophy of the lung may show little or much distention of the vesicles.

Small-lunged emphysema is frequently overlooked. Riesman, in his clinics, has called particular attention to this condition. Occurring in the absence of pulmonary fibrosis it probably often represents a congenital hypoplasia of the lung. A phthisical appearing, flat-chested, ill-nourished, and poorly developed young person may show poor expansion of the chest, low diaphragm, absence of heart and liver, dulness and poor breath sounds, and rib margin movements indicating an extreme degree of emphysema, and have the condition overlooked simply because the barrel chest and body contour which we commonly associate with chronic emphysema are not present.

Emphysema is not a specific disease, but a condition dependent on a combination of lung atrophy and vesicular overstrain, and the so-called different types are essentially the same. The emphysematous lung may be small because the lung was underdeveloped before emphysema supervened, or in pulmonary fibrosis we may find a small lung in which all the pulmonary tissue which is capable of expansion is extremely emphysematous, but most of the lung is fibrous and incapable of expansion. In senile atrophy the lung may remain small through lack of strain, because the respiratory muscles do not exert enough force to strain the lung, or through fibrosis.

Acute emphysema was important in certain pneumonias during the influenza epidemic. It also depends on weakening of the structure of the vesicle and overstrain by the severe and harassing cough. The mechanism of production and the results are thus identical with those of chronic emphysema. Whether this weakening occurs through bronchiolitic interference with the blood or nerve supply or through the toxic action of a virus is not known certainly, though it seems probable that the latter is a factor. The confusion of physical findings is also the same as in the chronic type. Early signs of consolidation are completely masked by the overdistended lung. It is important to remember that in bronchopneumonia even large consolidation may give no dulness on percussion.

Interstitial emphysema of the lung when described is usually mentioned as a curiosity which can be recognized only when the air has escaped from the chest into the subcutaneous tissues of the neck, face, or trunk, and as a condition without clinical importance. This condition was carefully observed during the influenza epidemic and proved to be extremely important in the course of influenza pneumonia.

Interstitial emphysema of the lung rapidly develops into mediastinal emphysema. From the mediastinum air may find its way along the great veins into the neck tissues and thence along the veins to the face, trunk, and arms. From the mediastinum air may also travel to the back by the azygos veins and to the lower extremities along the femorals. This subcutaneous

edema is clinically important in that the escape of air from the mediastinum relieves tension there, and at times gives great relief to the patient. The underlying mediastinal emphysema is a serious condition, in that it obstructs the return of blood to the right heart and produces a profound venous stasis. It is apparently the direct cause of death in many cases of influenza pneumonia.

Interstitial emphysema of the lung has been well demonstrated by the roentgenologists. Emphysema of the mediastinum in the course of influenza bronchopneumonia can be demonstrated by symptoms and physical signs, and in cases of mediastinal emphysema the development of subcutaneous tissue emphysema can in some cases be foretold by characteristic pain and tenderness above the clavicles before the air becomes apparent in the tissue.

You will notice a peculiar contour of the lung root shadows in these two x-ray plates of chests in which mediastinal emphysema was present, as compared to these other chest plates of cases of influenza pneumonia without the emphysema. In all the root shadows are dense. Ordinarily the root shadows lie close to the heart shadow and extend downward and outward in a comparatively straight line. With mediastinal emphysema you will note that the shadows stand away from the heart and are strongly curved, with the convexity outward.

Grosh and I described this acute emphysema in bronchopneumonia at one of the camps. Dr. Grosh was able in a case seen in civil practice to foretell the onset of subcutaneous emphysema. Luecké has also reported the pathologic findings in cases of subcutaneous emphysema.

SUMMARY

Emphysema as ordinarily seen represents the result of degeneration or atrophy of the lung tissue plus strain. Bronchitis, dyspnea, and cough are the commonest factors in its causation. It develops rapidly in cases of bronchiectasis.

It is usually complicated by persistent bronchitis and dyspnea.

The different types or classes of emphysema are essentially similar, all depending on disease of the lung structure and overstrain, except pure compensatory emphysema, which may be simply an overstretching of sound, healthy lung tissue due to contraction or collapse of other portions of the lungs. The term "hypertrophic emphysema" is misleading and erroneous.

Percussion and auscultation signs may be variable, areas of dulness and hyperresonance appearing and disappearing, particularly after deep breathing or coughing. This is well seen in a good proportion of examinations of subjects with extreme emphysema.

Emphysema covers up and complicates the physical findings in pulmonary conditions. This must constantly be borne in mind in the examinations of patients with chronic chest conditions or with severe acute bronchitis. Acute emphysema may mask the physical signs of a bronchopneumonia.

Severe emphysema may be found in flat-chested individuals.

Interstitial emphysema of the lung rapidly results in mediastinal emphysema, which may be a serious complication of bronchopneumonia. The latter condition is demonstrable by clinical signs and by x-ray findings.

Emphysema complicates x-ray diagnosis of pulmonary conditions. A comparatively short exposure is necessary in order to bring out satisfactory lung detail in an emphysematous chest. Portions of the lung may be in motion while the chest is stationary on account of unequal distention on inspiration, which tends to equalize itself while the breath is held.

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THE TREATMENT OF HYPERTHYROIDISM BY RADIATION

THE treatment of hyperthyroidism and exophthalmic goiter by radiation extends over a period of many years. Among the very first to treat this condition was Williams, of Boston, who noted marked improvement in a case of exophthalmic goiter from x-ray treatment and recorded it in his book, "The Roentgen Rays in Medicine and Surgery," 1902. I treated and recorded my first case in 1905 and, together with Dr. M. C. Thrush, presented the case before the Philadelphia County Medical Society February 14, 1906, published in the Therapeutic Gazette March 15, 1906. In 1915 my former assistant, Dr. Zulick, and I reviewed this subject up to that date, both as to our own work and that of others. It is during the past five years (and more especially during the past two years) that the general profession has come to recognize the value of this treatment. The amount of work done in this line during the past five years has increased several hundred per cent.

For example: Dr. Joh. Fred. Fischer, of Copenhagen, reported in 1916 upon 94 patients suffering from morbus basedowii (Ugeskrift for Laeger, No. 41). At the same time he emphasized the fact that considerable obscurity and uncertainty still prevailed in this branch of the Roentgen treatment which, at that time, according to his opinion, was not used to the extent it certainly deserved. Recently (Acta Radiologica, vol. i, fasc. 2, No. 2, September 20, 1921) he has made a report upon an experience with 490 patients, or approximately 500. In 1916 all of

his patients were treated in his private clinic. Since then 104 patients have been treated in his clinic at the Kommunehospitalet and 61 at the Bispebjergs Hospital. During the same time he treated privately 231. These, added to his first 94, makes a grand total of 490. This record serves as a good illustration of the growth and recognition of the value of radiation in the treatment of morbus basedowii. This same growth is recognizable in America, England, France, and Germany. Excellent reports have been made in America by Russell H. Boggs, of Pittsburgh, Augustus Simpson, of Washington, George W. Holmes, J. H. Means, and J. C. Aub, of Boston, Florence A. Stoney and Thurston Holland, of London, and many others.

The diagnosis of hyperthyroidism is not always easy and should be investigated so far as possible from every standpoint. Probably the most valuable means of diagnosis is the metabolism test. At least this seems to be accepted as the most reliable gage as to the degree of hyperthyroidism. Unfortunately, this test involves confinement of the patient in the hospital over a period of twenty-four hours, or at least over night, a certain amount of starvation, and considerable expense, which interferes with its general adoption as a means of diagnosis. Not nearly all hospitals possess equipment suitable for this examination, nor trained investigators capable of making the tests. Fortunately, our institution is equipped for this work, but not all patients (especially the milder type who are able to work) are willing to give up the time or go to the expense necessary for such an investigation. We shall, therefore, have to depend upon the clinical signs and other symptoms in most instances.

The quinin-hydrobromid test, recommended by Dr. Bram of this city (*Diagnosis of Exophthalmic Goiter by Quinin*, Med. Rec. 1920, xcvi, 887, Abs. Surg., Gyn., and Obst., March, 1921, p. 187), seems to have considerable value, and I believe can be used without harm. I have used it in some instances in which the diagnosis was undoubted, and in some other cases in which the diagnosis was doubtful. The test seemed to give me satisfactory results. I first tried the test on myself and my associates, and then used it on patients. Briefly, the test con-

sists in the administration of quinin-hydrobromid in 10-grain doses three or four times a day. In the normal person there will be a pronounced cynchonism after the administration of from two to six or eight doses, but the hyperthyroid patient can take this continuously for weeks. Since the quinin-hydrobromid is used in treatment in half this dose, we must assume that it will do no harm, and it is a test that is worth making.

The Goetsch test is very interesting as a demonstration, and can be used even as a partial gage during the progress of the treatment, but it involves some risks and at times seems to make the patient distinctly worse. In some instances, as records show, a patient who borders on hyperthyroidism is hurried into a definite paroxysm and develops undoubted symptoms.

The tachycardia is a very important symptom, and if other causes of tachycardia have been eliminated this symptom becomes a strong factor in diagnosis, and the study of the pulse is certainly the most convenient guide during treatment. One must, however, examine the pulse both at rest and after exertion or excitement in each instance. Since mental excitement as well as physical exertion will cause a rapid rise in the pulse-rate in these patients, it is not always possible to obtain the record during repose, especially in the ambulant patient. However, if one counts the pulse with the patient lying quietly in bed (in the case of a bed patient), and then allows the patient to sit up, there will be a much greater rise in pulse-rate with this amount of exertion than is obtained in other patients. If the pulse is already high and gives very little additional rise upon slight exertion, one will usually find that the original count was not made with the patient in a quiet condition. So, too, with the ambulant patient, in whom one usually studies the pulse in the sitting posture and at rest, there will be an abnormal increase in the pulse-rate upon slight exertion, such as standing or walking two or three times across the floor. If both these tests, at rest and after exertion, are made each time the patient is examined or comes for treatment, it will form a valuable gage as to the progress of the case providing other true cardiac disease has been eliminated.

One may have exophthalmos in patients without goiter, and there are many patients in whom one or more of the classical symptoms of exophthalmic goiter are missing.

The Indications for Radiotherapy in Hyperthyroidism.—I believe the best plan, when practical, is that adopted by the Massachusetts General Hospital, by which each patient is investigated by a conference of an internist, a surgeon, and a radiologist, and together they decide upon the best form of treatment in the individual case. From time to time these patients are reviewed by this same group of physicians so that a fair judgment may be made as to the progress of the case, and as to whether any particular form of treatment shall be continued. At each of these conferences special attention is given to the pulse-rate, the weight, and the metabolism rate, these records being made approximately once a month while under radiation treatment, and, in fact, also after either medical treatment or surgical treatment. As a result of a study of a series of cases in this manner Dr. Means and Aub conclude that the chance of cure in exophthalmic goiter is as good with Roentgen-ray treatment as with surgery in groups of cases of equal toxicity, and that being true, the former method is preferable, for the danger of fatal outcome is less (*Archives of Internal Medicine*, December, 1919, vol. 24, pp. 645-677). Of the 9 known deaths occurring in their original series of 55 cases, 5 were directly the result of surgery. One patient after prolonged Roentgen-ray treatment finally died of exophthalmic goiter; 3 patients died of unknown cause, 1 of these after having been apparently cured by operation, 1 after having been apparently cured by the Roentgen ray, and 1 after failure to improve materially under roentgentherapy.

In comparing the value of surgery with radiotherapy it must be borne in mind that generally the more severe type of patients are treated by radiotherapy because there is some risk involved in the operation. In other words, the surgeon generally selects the patients that he feels will stand an operation, while the radiologist is likely to treat all as they come. More recently the patients are coming earlier for radiotherapy with the hope of avoiding an operation. In only 3 of the patients that I have

treated has operation been done. In 1 of these the operation was done for economic reasons with the object of hastening the result and getting her out of the hospital to her home (after two months), but not because of any failure of treatment. She had shown definite improvement. In the other 2 x-ray treatment was abandoned because of impatience, and with the object of hastening the result. In choosing between surgery and radiotherapy we must keep two factors in mind: First, the surgeon removes a portion of the gland and thereby reduces the total quantity of glandular tissue capable of producing hypersecretion, or the abnormal secretion. Much depends upon his judgment as to the quantity of tissue removed. If too much tissue is removed there is danger of hypothyroidism. If too little tissue is removed there is danger of recurrence of the symptoms, and both these results are well known to have occurred following excision. These operations are attended by some risk, and for this reason the worst cases are usually not operated upon. In this severe type the surgeon frequently does a ligation with the object of reducing nourishment of the gland and thereby reducing the secretion, which may permit the patient to regain sufficient strength to withstand an operation. There is always a certain amount of shock incident to the operation, but when the operation is successful the results are more prompt than those obtained in radiotherapy. Second, when radiotherapy is depended upon the results are obtained comparatively slowly and improvement is not usually noticed until at about the end of a month. Therefore, when the symptoms or circumstances demand quick results, surgery is to be preferred providing one keeps in mind the above risks and conditions. On the other hand, by using radiotherapy in the moderate case the patients avoid a long stay in the hospital, and very generally can go about their usual occupation. In the more severe type the patient should, of course, be kept at rest so far as is practical. The time required to produce satisfactory results is six months to a year, but patients do not usually object to this delay because of the usual improvement recognizable at the end of a month and the progressive improvement from that time.

Results of Treatment.—(1) *A decrease in the pulse-rate* is one of the first results to be expected, and this change is usually noted within the first month. The reduction is usually from 5 to 10 beats per minute, but may be as much as 25. In estimating this pulse value it is always important to make a record of the pulse with the patient at rest, and again after slight excitement or exertion, such as walking across the floor three times, or if the patient is in bed an estimate with the patient lying on the back and again after sitting up. If this double record is made at the end of each month it will form a fair gage of results, and in nearly all instances there will be a progressive improvement. I believe that it is inadvisable to continue to treat patients until the pulse has returned to normal, for there is a delayed effect of the rays due to the progressive atrophy of the glandular tissue which may lead to hypothyroidism if the treatment is continued until the pulse returns to normal. (2) *Increase in weight.* In practically all instances there will be obtained a history of progressive loss of weight, in some instances little, and in other cases much. If there has not been a great loss of weight there will, of course, not be a great increase in weight. This increase in weight is usually noted at the end of the first month and when the patient comes for the second course of treatment. (3) *Decrease in the nervous symptoms.* There will be a lessened excitability, a decrease in the sleeplessness, a lessened tendency to worry, a decrease in irritability. (4) *Attacks of diarrhea will become less frequent.* Sweating and other vasomotor disturbances will be decreased. Glycosuria, which is present in about 3 per cent. of the patients, disappears. In some cases an attack of diarrhea or glycosuria may follow temporarily shortly after a course of treatment. In most instances at the end of a month the patients will state voluntarily that they are "feeling better." (5) *The thyroid enlargement is among the last symptoms to disappear,* but since the object of the treatment is not primarily to reduce the thyroid in size, we are not so much concerned about this symptom. Generally there is no appreciable reduction until after the end of two or three months. In many instances the thyroid enlargement disappears completely. Much will

depend upon the duration of the thyroid enlargement. If the hyperthyroid symptoms have been superadded to a previously existing enlarged thyroid of long duration there will be only a moderate reduction in size and the thyroid enlargement will probably at no time disappear completely. If, on the other hand, the thyroid enlargement occurs conjointly with the symptoms of hyperthyroidism the enlargement will probably ultimately disappear completely. (6) *The exophthalmia is the last symptom to disappear.* There is usually some reduction in the exophthalmia at the end of six months or a year, but the treatment should at no time be continued merely to cause a disappearance of this symptom, and it has been my experience that this symptom continues to disappear gradually over a long period after treatment has been discontinued.

The *duration of these results* are generally permanent. The patients continue to report themselves as feeling perfectly well over a period of many years. I have treated approximately 220 cases of goiter and hyperthyroidism, and in only a few instances have the patients had a relapse. The treatment produces its results theoretically by bringing about an atrophy of the glandular tissue. By some it is supposed that the rays bring about a change in the compound of the secretion as well as a diminution in the total quantity. In a few patients there has developed during the course of treatment a hoarseness, and in one case aphonia. This symptom may last from one to several weeks. Recently we are cautious in protecting the larynx from radiation (at least the upper portion of the larynx), and do not permit the rays to reach the tissues higher than is absolutely necessary. It is impossible to know whether this change in technic has done any good, for the symptom has not developed in more than about 1 per cent. of the patients. Dr. Fischer, of Copenhagen, has also called attention to this symptom. It is my opinion that, in general, radiotherapy is the best form of treatment for toxic goiter.

Technic.—During the fifteen years in which I have been using radiotherapy in toxic goiters there has been a progressive change in the technic, and little is gained by discussing all the stages

through which we have passed. At the present time the patient is placed in the supine posture with a pillow under the neck and the head thrown well back. Treatment is given through four portals of entry. The thyroid and thymus regions are divided in the median line. A horizontal line is drawn above the thyroid enlargement extending outward from the median line on each side. A second vertical line is then drawn downward and outward obliquely, beginning about $2\frac{1}{2}$ inches to the outer side of the median line. Treatment is then given through the two central fields, directing the rays downward and inward, thereby obtaining some "cross-firing" effect on the deeper portions of the gland and the thymus. The patient is then placed in the prone position, face rotated toward the side being treated, and treatment is given through the posterior two fields, directing the rays downward and inward. In this way the greatest amount of cross-firing effect will be obtained with the least effect on the skin. These four treatments are usually given in one day, and only in the exceptional case is it divided. No increase in symptoms and no harmful effect has been noted by me following this treatment, though in two or three instances on record patients are supposed to have been made worse by the treatment. We believe that these instances are more likely coincidental exacerbations of the disease previously existing rather than that the rays have caused them to be made worse. Such opinion is also expressed by Fischer. These cases which were made worse or died also belong to the severe type, in which such exacerbations and even death may occur rather suddenly no matter what form of treatment is used. Through each of the areas above described are given about 75 to 80 per cent. of an erythema dose filtered through 6 mm. of aluminum and from a distance of 25 cm. The erythema dose is varied somewhat with the individual, but the factors making up this dose will vary considerably according to the installation, and therefore each operator should learn his erythema-dose value with his own installation, either measured biologically or by physical means.

The interval between the first and second course of treatment is usually four weeks. In urgent cases the treatment may

be repeated, I believe safely, in three weeks. After this it should not be repeated inside of four weeks, and as soon as the symptoms approach normal the interval should be gradually lengthened so as not to carry the effects too far. Generally after the third or fourth series I increase the interval to six- and then to eight-week intervals. Judgment must be used in this matter, and the symptoms of the patients and their habits must be kept carefully under control. As associated treatment it is first of importance to eliminate any focus of infection, and unless this is done the treatment may be very much and unnecessarily prolonged. In fact, with some patients the results are not satisfactory until all such infection has been removed. The patient should be deprived of any stimulants, and all physical or mental excitement avoided so far as possible. The administration of quinin-hydrobromid in 5-grain doses three times a day may be helpful, and in some patients it is used. All other general medical treatment such as has been found successful by the internists should be utilized.

Radium in the Treatment of Hyperthyroidism.—Radium has been used less extensively in the treatment of hyperthyroidism or goiter because it is less widely distributed, and I think less definite technic has been developed in its use, though, of course, the most exact technic is capable of being developed with radium, even more satisfactorily than that of the Roentgen rays. It seems to me, however, that the place for radium particularly is in the group of patients who are bedfast and whose symptoms are so severe that the exertion and excitement incident to moving them to the Roentgen laboratory is definitely detrimental. Radium can be applied to these patients without any excitement or apprehension and may even be applied without the patient's knowledge, providing one first makes an application of some sort of innocent dressing and then replaces the innocent dressing with the active radium. Very excellent work has been done along this line by Dr. Aikens, of Toronto, Canada (*Radium in Toxic Goiter*, *The American Journal of Roentgenology*, July, 1920). He has made a report on approximately 100 cases of this disease, 16 cases in 1915, 45 cases in 1918, and finally a

report on 100 cases in 1919. I will quote the following extract from his article:

"In applying radium over the thyroid gland the effect required is one of deep penetration with a minimum skin reaction. In order to attain this result the radium must be so screened as to prevent the action of the short but powerful beta rays, and to obtain the benefit of the more penetrating gamma rays.

"The form of applicator which I prefer is large and flat. In some cases I have used tubes, but I consider the flat applicators much more satisfactory. Those I use most frequently are 4 x 4 cm., containing 10 mg. radium element, but I have two others which also give satisfaction, one 2 x 2 cm., containing 10 mg. radium element, and the other 4 x 2 cm., containing 5 mg. radium. The plaques are screened with two thin aluminum screens or one fairly thick brass one (about 0.8 mm.) with a layer of felt.

"As a rule I make applications of three hours' duration, giving a first treatment of from 150 to 360 mg. hours, depending on the degree to which the disease has advanced. I find it preferable to give smaller doses rather frequently than concentrated heavy dosage, as the latter is much more apt to cause systemic disturbances. The first treatment is usually completed in three days, and I leave an interval of about six weeks between applications. If the disease makes good progress, the second treatment need not be so heavy as the first. The quantity given in the second and subsequent treatments usually varies from 50 to 150 mg. hours."

Drs. Burrows and Morrison (The Treatment of Exophthalmic Goiter by Radiation, Proceedings Royal Society of Medicine, London, 1920, vol. 12) have made a report on 200 cases, 100 treated by radium and 100 treated by the x-rays. They made use of 2.5 mgm. of radium per square centimeter and used from 50 to 100 mgm. made into a plaque, filter 1.5 to 2 mm. of brass, plus 24 to 36 layers of black photographic paper kept over the gland twenty-four hours, repeated in six weeks. They found that heavy treatments at intervals were better than smaller treatments more frequently. They say that after twelve months,

even if the skin is normal, they think it is advisable to omit treatment once in a while. In 100 consecutive cases treated by the Roentgen rays the results were perfect, with no symptoms in 27, good functional results in 49, improvement in 20, gave up treatment 4; 100 cases treated by radium gave perfect results 20, good functional results 20, improved 40, gave up treatment 20.

I have made up a plaque of 10 mg. needles and have used 100 mg. very much as described by Burrows and Morrison.

The following few cases taken at random will illustrate the results that are obtained:

Case I.—Miss D. Referred by Dr. H. M. Eberhard, September 30, 1915, suffering from violent tachycardia (at times running as high as 150 to 160), with a moderate sized enlargement of the thyroid. There was no improvement under any form of medication or even from rest in the hospital. She had marked tremor, exophthalmos, pulse 153 on arrival, weight $107\frac{1}{2}$ pounds, systolic pressure 178. Symptoms had continued for two years. Menstruation was irregular. α -Ray examination showed some slight cardiac enlargement with some evidence of a persistent thymus. On September 30, 1915 she was given one dose of α -rays, 15 milliamperes minutes, 9-inch spark gap, 8-inch distance, 5 mm. of aluminum filter. October 14th she received three such doses amounting to approximately two-fifths of an erythema dose over each area. At this time her pulse was 147, weight 110 pounds. On November 4th the above treatment was repeated, pulse 144, weight 109 pounds. December 2d pulse 116, weight 109 pounds. The three portals of entry were again given. Even after exertion, her pulse only went to 122. January 6th pulse 92 at rest, 102 after exertion, weight $115\frac{1}{2}$ pounds. Three portals of entry treated as before. February 12th pulse at rest 94, under exertion 102, weight 115 pounds; 2 doses similar to the above were given. March 25, 1916 pulse 102, after exertion 120, weight 116 pounds. Three areas treated. May 20, 1916 general health greatly improved. Expressed herself as feeling fine. Weight 117 pounds. Pulse on arrival and after some exertion 114. July 15, 1916 general appearance nearly normal, feels well, eyes slightly prominent, goiter nearly disappeared,

pulse 94 after slight exertion. Menses were normal. September 9, 1916 pulse 84, after exertion 88. Still tires easily. Menses prolonged. December 2, 1916 pulse at rest 94, on exertion 116, weight 118½ pounds. Four doses given. A few hours after this treatment the patient called on the telephone and said that the side of her jaw had become so swollen that she could hardly open her mouth. In several instances there has been swelling of the parotid following x-ray treatment about the head and neck. This usually disappears within twenty-four to forty-eight hours without any treatment, but at first sight it gives the impression of mumps. December 3, 1917 the patient looked almost well. Goiter not noticeable or palpable. Pulse 80 at rest, 102 on exertion. February 4, 1918 no treatment. Pulse 80 sitting at rest; standing, 90. Looks well and feels well. April 22, 1918 patient looks well, feels well, no goiter, no exophthalmos. July 8, 1918 pulse 90, looks perfectly well, feels well, but has a low resistance. June 27, 1919 weight 110½ pounds, pulse 96 after slight exertion in coming to the office. Looks well and feels well. No treatment. May 14, 1920 general condition excellent, pulse 98, weight 113 pounds. June 20, 1921 pulse 88, weight 119½ pounds, feels well, and looks entirely well. Skin about the neck entirely normal. No evidence of exophthalmos. No tremor. Thinks she still has less endurance than normal.

Case II.—Mr. A. W. C., age forty-two, referred by Dr. J. M. Anders, September 17, 1918. Eight years previously he had severe localized headache on the right occipital region and his hair fell out over the area affected. Headaches disappeared under medical treatment. February, 1917 this headache recurred and has continued. March, 1918 had a collapse. Lost 16 pounds in weight. At this time weighed 97 pounds. Normal weight 152 pounds. August, 1918 noticed swelling of the thyroid gland. He had prominent eyes for a year. Pulse 120. His thyroid and thymus area were treated through four portals of entry, as described under technic. Examination of the teeth at his first visit showed evidence of infection about two of the roots, and open cancellous spaces about the several areas of pyorrheal absorption. He was given thirteen such series of

treatments in thirteen months. He was given two such treatments during the next year, when his pulse had dropped to 84, his heart action had become strong and regular, the eyes had partially receded, the goiter had disappeared. He will likely continue to improve as he has during the past year without further treatment. The eyes are gradually receding and all other symptoms have practically disappeared.

Case III.—Miss A. S., age sixty, referred by Dr. Robert Pitfield, December 14, 1920. Patient was extremely nervous, irritable, and mentally disturbed. Pulse was 140, exophthalmos marked, thyroid enlarged, weight 117 pounds. α -Ray examination showed abscesses at the roots of the left upper second and third molars. Examination of the tonsils by Dr. Fetterolf showed them to be small and only mildly septic. Metabolism was 25 above normal. She was given six courses of treatment within six months. At the end of this time her pulse was 80, weight 136 pounds, skin of the neck normal, looks well, feels splendid. The metabolism was then only 8.2 above normal. When seen two months later her weight was 142 pounds, pulse 88; her mental condition was practically normal. She will be kept under observation. Metabolism tests will be made from time to time, and I am expecting her to get entirely well. She has not been treated since June, 1921.

CLINIC OF DR. THOMAS C. KELLY

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DISSECTING ANEURYSM OF AORTA

GENTLEMEN: I wish to present to you today a case interesting not only for the comparative rarity of the lesion involved but also for the well-marked physical signs which can be elicited.

W. H., a negro aged forty-two years, and a laborer by occupation, was admitted to the Medical Wards of the Philadelphia General Hospital, on the service of Dr. Stevens, to whom I am indebted for the privilege of presenting him. He came to the ward complaining of swelling of the left shoulder posteriorly, cough, night-sweats, loss of weight, and nocturia. His present history is as follows: About eight weeks ago he developed a persistent cough with expectoration, which on several occasions contained small amounts of blood. The cough is still present with but little change either in the character or amount of the sputum. About four weeks ago he noticed a small swelling about the size of an egg along the vertebral border of the left scapula, which for two weeks increased rather rapidly in size, but which since then has remained more or less stationary. This swelling is painful—the pain being, as he describes it, rather “biting” in character, and appears usually at night, in paroxysms of half an hour’s duration. Since the appearance of the swelling the patient has had several night-sweats, and believes that he has lost about 10 pounds in weight during the past two months. He also has had to urinate about four or five times a night during the course of this illness.

Previous Medical History.—As far as he knows he suffered the usual diseases of childhood. About two years ago he was treated at this hospital for acute pleurisy of the left chest (possi-

bly preceded by pneumonia), being aspirated twice, with negative results. Since this time he has been perfectly well until the beginning of the present illness.

Family History.—This is vague and unsatisfactory, as outside of the fact that his father, mother, and one brother are dead, he knows nothing of any illness in his family.

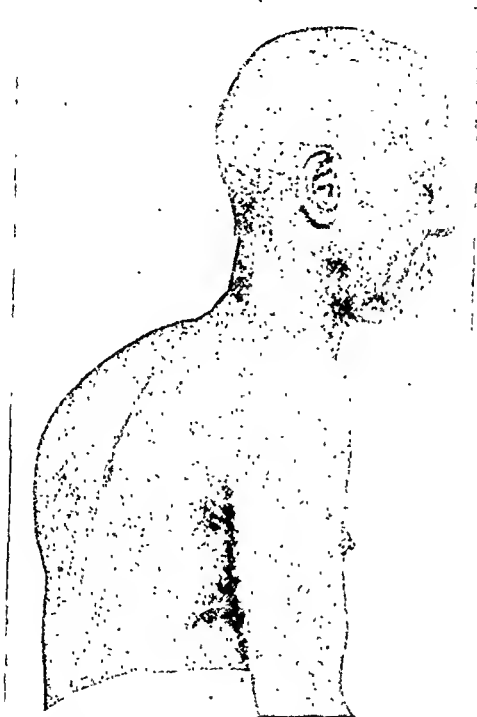


Fig. 159.—Aneurysm of the descending arch of the aorta. Lateral view of patient showing bulging of left side of chest posteriorly.

Before proceeding to the physical examination of the patient let us consider briefly the possibilities suggested by the above history. Here we have an adult negro, complaining of cough with occasional bloody expectoration, night-sweats, loss of weight, and a painful swelling in the region of the left scapula, with a previous history of pleurisy of the left chest two years ago.

As you are aware, the two most common causes of cough with bloody expectoration are pulmonary tuberculosis and valvular disease of the heart, although it is not infrequent in aneurysm of the arch of the aorta, where there may be more or less frequent hemoptysis, even some time before a fatal termination of the disease, and may occur in such conditions as purpura, hemophilia, etc. Night-sweats, while being a symptom one usually associates with tuberculosis, may occur in many other diseases, such as syphilis (gumma of liver), cardiorenal disease, acute rheumatic fever, pyemia, or pus collections, etc., although in some of the foregoing the sweating may be present during the day as well as the night. Loss of weight occurs in so many of the so-called chronic or debilitating diseases, as well as the acute severe infections, that its presence as a symptom should be considered only in a confirmatory character. The presence of the swelling in the back opens up several interesting possibilities as to its cause, which could best be intelligently considered when an examination of the chest has been made, although the previous history of pleurisy (possibly as an accompaniment or sequela of pneumonia) should be borne in mind as having some possible bearing not only on the cough, but the tumor formation, as many of the so-called unresolved pneumonias with pleurisy are really multiple small (sometimes large) pulmonary abscesses.

With these possibilities in mind, and proceeding now to the physical examination, we learn that it was noted on admission that the patient was a fairly well-nourished, but anemic looking negro. No jaundice or edema present. There was marked clubbing of the fingers, which the patient states has developed recently. The pulse was weak, regular, and apparently equal on both sides. The pupils are equal and react somewhat sluggishly to light and accommodation. The tongue was heavily coated, but showed no tremors or fissures. The teeth were in filthy condition, many necrotic areas being present, especially at the bases of the lower teeth. There were a few small movable glands noted on the left side of the neck, the trachea was displaced to the right, and a tracheal tug was present. The heart was displaced to the right, the apex being at the left sternal line,

and the right border being about the right midclavicular line. The heart's action was regular, sounds were weak, there was a systolic murmur heard at the apex, and a diastolic murmur and a diastolic shock present at the aortic area. The examination of the chest is interesting. On the right side anteriorly the



Fig. 160.—Aneurysm of the descending arch of the aorta. Posterior view. Arrow points to erosion of the skin occurring ten days before the death of the patient.

breath sounds were somewhat weak and distant, and a few subcrepitant râles were heard at the apex. Posteriorly, Grocco's triangle was not present and the same râles were heard above the spine of the scapula. On the left side anteriorly there was flatness to percussion from the third to the sixth rib, and also laterally. Over this area tactile fremitus, vocal resonance, and

breath sounds were absent, and above this area numerous râles and friction sounds are present. Posteriorly on the left side there is a large, pulsating tumor, horseshoe shaped, following the vertebral border of the scapula downward to the eleventh rib, and extending laterally to the midaxillary line. Over this mass no ribs could be palpated except at the borders. The remainder of the physical examination is practically negative. On admission his temperature was 98.2° F., his pulse 80, and respirations 25 per minute.

Bearing in mind one of the possible diagnoses suggested by the history alone—tuberculosis—we find that the patient on examination showed the presence in his chest, at the apices of his lungs, of numerous râles, although over these areas there was no impairment of resonance nor bronchial (or bronchovesicular) breathing; so that while there may be some tubercular involvement of the lungs (with the possibility of tuberculous pleurisy of left lung—râles and friction-rubs), the more likely diagnosis is bronchitis (with bronchiectasis), associated with the more serious condition of the left chest posteriorly (the pulsating tumor). The results of the examination of the heart in conjunction with the findings we have just considered from the lungs do not, I think, warrant us in explaining this patient's symptoms from his cardiac condition, as one can hardly suppose that he would have hemoptysis, night-sweats, and loss of weight from a cardiac condition which gave rise to no other signs of decompensation—there was no edema, no ascites, no enlargement of the heart or liver, nor any marked dyspnea.

Coming, then, to the swelling, of which the man made principal complaint, and which we have seen as a pulsating tumor involving the greater part of the posterior aspect of the left chest, let us consider what might give rise to such a condition. Sailer¹ in 1904 collected from the literature 97 cases of pulsating tumors of the chest which comprised five groups of cases: 1, Pulsating empyema and pulsating pyopneumothorax of necessity; 2, pulsating empyema and pulsating pyopneumothorax; 3, pulsating encapsulated empyema; 4, pulsating serous or hemorrhagic effusion, and 5, pulsating extrapleural abscess. Levi²

in 1914, in a series of 110 cases of pulsating effusions of the thorax, found that the left chest was involved in 93.6 per cent. of the cases. Suggestive of pulsating empyema (or effusion of other character) in this case is the previous history of pleurisy of the left chest, although one can hardly imagine a man suffering from a pulsating tumor of that variety which would attain the size of this, without more symptoms referable to the respiratory tract. Let us consider, then, what, in this case, is the most likely diagnosis, that of aneurysm of the descending arch of the aorta, saccular in character, possibly dissecting, which has so grown and extended itself as to reach the form and size you see. Supporting this view there is, first, the age and race of the patient (negro in middle life, with sluggishness of the pupillary reactions—probably syphilitic, and therefore prone to develop an aneurysm); second, the character of the pain in the tumor—"biting" in character, usually occurring at night; third, the presence of a diastolic murmur and a diastolic shock at the aortic area (the heart being pushed to the right), and lastly (which point I have purposely not emphasized before), the presence of a tracheal tug. And now let us see if the laboratory is of aid in supporting our diagnosis. The urinary examination was practically negative. The blood examination showed: Hem. 36 per cent., R. B. C. 2,376,000, and W. B. C. 11,000, of which the differential count gave polymorphonuclears 77 per cent., small lymphocytes 12 per cent., large lymphocytes 6 per cent., and large mononuclears 5 per cent. The Wassermann reaction was reported strongly positive. The examination of the sputum for the presence of tubercle bacilli was negative. The x-ray report was as follows: "Dense shadow filling lower two-thirds of left chest. What is apparently heart is displaced markedly to the right. The upper third of left chest has much less air-bearing space than right side. Diagnosis: Aneurysm of arch of aorta (dissecting)."

In an extensive statistical analysis of aneurysms, based on the study of 12,000 autopsies made in the Philadelphia General Hospital and the Hospital of the University of Pennsylvania, Lucke and Rea³ found 321 aneurysms occurring in 268 subjects,

or 2.2 per cent. of the patients examined. In their series aneurysm was relatively more common in the negro than in the Caucasian

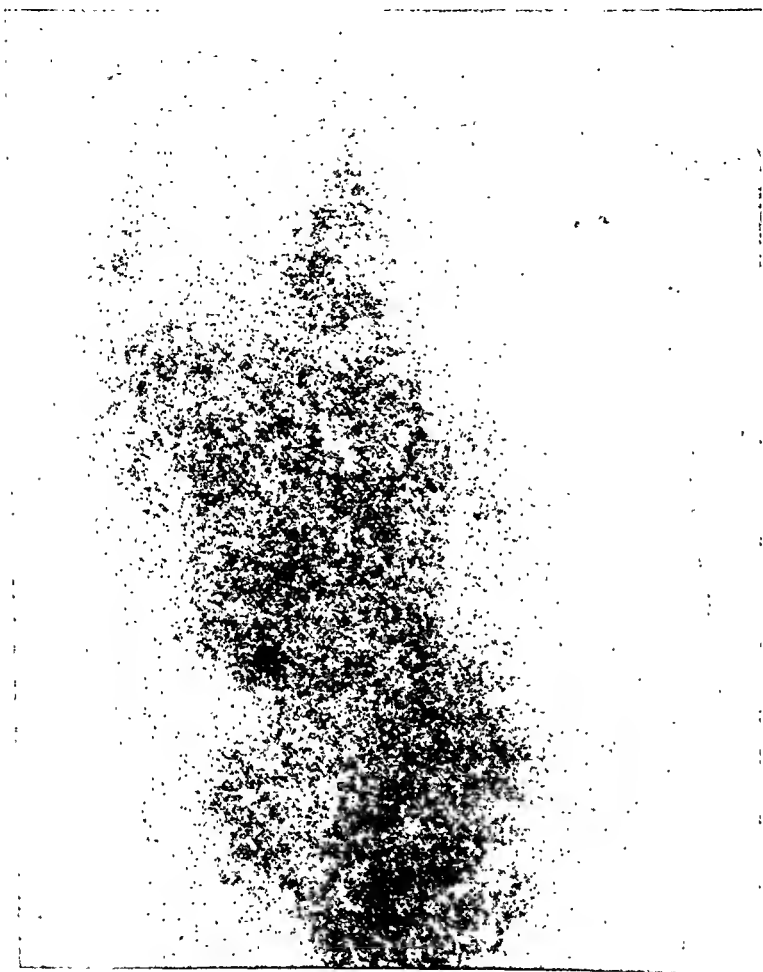


Fig. 161.—Aneurysm of the descending arch of the aorta. x-Ray view showing dense shadow of lower two-thirds of left chest. Heart pushed over to the right.

race, occurred four times more frequently in males than in females, and at an earlier age (most frequent in the fourth and

fifth decades) in negroes than whites. The aorta was most often involved (278 out of 321 aneurysms). In an analysis of 953 cases of aortic aneurysms Hare located 570 in the ascending, 104 in the transverse, and 110 in the descending portions of the aorta.

Aneurysms involving the thoracic aorta may be divided into five classes⁴: 1, Aneurysm of the intrapericardial portion of the arch and sinuses of Valsalva. In this situation the aneurysm is usually small and deeply situated, and during life the clinical picture is apt to be that of angina pectoris or aortic insufficiency. If it compresses the superior vena cava there may be, in addition, congestion of the face, or undue fulness of the jugulars and the veins of one or other upper extremity. 2, Aneurysm of the ascending arch, which includes that portion of the aorta between the sinuses of Valsalva and the orifice of the innominate artery (aneurysm of physical signs). In this situation aneurysms usually attain considerable size, extend upward and to the right (rarely to the left) of the sternum, and occasion dyspnea and varying degrees of pain, both usually increased by exertion. 3, Aneurysm of the transverse portion of the arch (aneurysm of symptoms). In this situation the aneurysms do not, as a rule, attain very great size and may project in any direction, usually, however, backward. Inequality of the pulses and pressure symptoms (dysphagia, dyspnea—occasionally paroxysmal in character, hoarseness, a brassy cough, and hemoptysis) are common. 4, Aneurysm of the descending portion of the arch. In this situation the aneurysm usually grows backward and may erode the vertebræ (or, if extensive enough, the ribs), but may compress the esophagus and rupture into it, or from pressure on the left bronchus cause bronchiectasis of the left lung. Pain may be the dominating symptom, and may be either dull and aching in character, or sharp and shooting, and may be localized along the vertebral column (whence the condition may be mistaken for Pott's disease), or radiate around the thorax and down the arm. 5, Aneurysm of the descending thoracic aorta. Aneurysms in this situation are rather uncommon, but when present usually extend backward with erosion of the vertebræ (rarely they extend forward, and if located above the diaphragmatic opening,

may occasion epigastric pulsation). Pain (of varying character and severity) and dysphagia are the usual symptoms.

Coming back to our case, the prognosis, as you can readily imagine, is fatal, and treatment directed toward the cure of the condition is futile. The character and extent of the growth, as well as the condition of the patient, render inadvisable treatment by wiring and electrolysis. This method of treatment, as advocated by Lorradi, and practised later by Rosenstein, Kerr, Hare, and others, has in many cases not only caused an amelioration of the symptoms with sometimes complete cessation of pain, but often a lessening in the size of the aneurysmal sac. This was beautifully exemplified by a man who two years ago was wired in this hospital by Dr. Sailer, and who returned last spring for observation. In the interval he has been free from all symptoms (unless he exerts himself immoderately), and his x-ray findings, as compared with those before wiring, showed a diminution of the size of the aneurysm of about 2 cm.

As regards treatment, much can be done to render the remainder of the patient's life more comfortable. Rest in bed (if necessary with a back-rest) is of prime importance and should be insisted upon, together with light, easy assimilable food, and proper attention to the organs of excretion. In this case, as in some others, where the mass itself would seem momentarily to be at the point of rupture, a support, in the form of a snug muslin bandage, would be of service. Of drugs, the iodid of potash in large doses is at times quite helpful (especially in those cases with undoubted syphilitic taint), and serves sometimes to relieve the pain, which in many instances is quite distressing. Simple tonics, such as *nux vomica* with bicarbonate of soda (and possibly gentian), may stimulate a jaded appetite. And lastly the judicious use of morphin may render more bearable what is, of necessity, a miserable existence.

Later.—Gentlemen. I am able today to present to you the completed record of the case of aneurysm, with the pulsating tumor of the back, whom you saw two months ago. The patient for a short time after your last visit seemed to feel better, as a result probably of the rest in bed and regulated mode of living.

Shortly thereafter his general condition became much weaker, his pulse-rate higher and its volume smaller, and the pain in the tumor became more constant and severe. About one month after his admission hoarseness of the voice (pressure on the left recurrent laryngeal nerve) developed and continued until the end. About two weeks before his death, while attempting to change a supporting bandage which had been applied to his chest, it was seen that a small erosion of the skin, about 2 cm. in diameter, had developed over the angle of the left scapula. His condition about that time became rapidly worse, his pain increased in severity and was more continuous, the mass increased greatly in size, and he finally died.

The autopsy findings, as recorded, are as follows: "Body of old black man with enormous mass protruding beneath and posterior to the left axilla. The skin over the center of the mass is eroded and no ribs can be palpated except at the edges of the mass. The peritoneal cavity contains no fluid and but few adhesions. The left pleural cavity was small, being pushed forward by the mass in the posterior mediastinum, and beneath the parietal pleura in skin. It contained about 75 c.c. of blood-stained fluid and both parietal and visceral layers were much thickened. In the right pleural cavity there were a few adhesions at the apex and a small amount of fluid. The posterior mediastinum was occupied by part of the aneurysm and the pericardium contained the usual amount of fluid and was small. The heart was pushed over toward the right side, the apex being about 1 cm. to the left of the left sternal line. It is not much enlarged. The left lung is collapsed, does not crepitate, and has a thickened pleura. In the lower lobe near the lower border there are several smooth-lined cavities communicating with a bronchiole. The rest of the lung was moist. The right lung was of good size, rather heavy, and when cut the cut surface was very moist. The spleen was of moderate size, capsule thickened, deep dark red, and soft. The suprarenals showed no gross lesions, and the kidneys were firm, capsule slightly adherent, surface smooth, cut surface bloody and dark red. The cortex and medulla are not as distinctly differentiated as usual. Ureters

and bladder: former normal, the later contains cloudy purulent looking urine. Stomach was of good size, walls distinctly thickened, rugæ prominent and firm, mucosa soft. Aorta: At the beginning of the descending arch there is a saccular aneurysm about 20 cm. in diameter. In the posterior wall there is a hole about 2 cm. in diameter which communicates with the large



Fig. 162.—Aneurysm of the descending arch of the aorta. Heart displaced to show view of aneurysmal sac. Arrow points to hole communicating with the large mass of left chest.

mass occupying the left side. This mass consists of clots of varying age. Pathologic diagnosis: Aneurysm of descending limb of aorta with atelectasis of left lung. Bronchiectatic cavities of left lung. Hypertrophic gastritis. Cystitis.

The literature on dissecting aneurysms has been collected and analyzed by Bostroem,⁵ Fleckseman,⁶ and more recently

by Franz Schede,⁷ to which MacCallum⁸ has added 5 interesting cases. Keilty,⁹ in a study of 71 aneurysm specimens from the museum of the Philadelphia General Hospital, found 9 cases of dissecting aneurysms of the aorta, in 5 of which there was erosion of the ribs. More recently I have gone over the records of this museum, and found that there were present specimens of 21 dissecting aneurysms, 11 of which involved the arch of the aorta, 3 the abdominal aorta, 2 the thoracic aorta, and one each the posterior tibial, the middle cerebral, the external iliac, the femoral, and the iliac arteries.

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CLINIC OF DR. THOMAS McCRAE

JEFFERSON HOSPITAL

THE DIAGNOSIS OF ACUTE NEPHRITIS

THIS patient entered the hospital a few hours ago, and it is not possible on this occasion to give you the results of a complete study. This is rather an advantage, as I believe a lesson can be learned by comparing our first impressions and the later ones as modified by the subsequent study. The special point of interest is the matter of diagnosis, which at first glance may seem to be a simple matter. There is a good rule in diagnosis which says, "Distrust the obvious," and it is perhaps applicable here. The history is as follows:

J. S., aged twenty-three, a huckster, comes complaining of swelling of the face and abdomen and a certain amount of pain in the back.

Family History.—This is negative except that one sister died of eclampsia.

Past History.—This shows extremely little of any account. The patient states that he had whooping-cough in childhood and is certain that this is the only acute infectious disease which he has had. He states that he has not suffered from throat or nose trouble and that, in general, his health has been extremely good. He has not had any disturbance of respiration or circulation, and his digestive tract has been normal. He entered the army in 1917, was in France on active service, and subsequently with the Army of Occupation in Germany. While in army service he states that he was perfectly well except for an occasional headache.

There is one other point in his history which may be put with his past history or included in the present illness. He states.

that in 1916 he was in bed for about two weeks with an illness of which the chief feature was swelling of the abdomen. He is not able to give us any more details than this.

Present Illness.—The beginning of this was fairly sudden six weeks ago. He first noticed that there was some swelling about the eyes, and subsequently this extended to the face. About a week ago swelling of the abdomen was noted, and recently he has had a good deal of pain, which, apparently, has been particularly in the back and flanks. There has been no shortness of breath, no swelling of the legs, and no disturbance in the digestive tract except slight constipation. He has had some headache, but this has not been extreme.

The examination brings out the following points: The patient is a large, well-nourished, sturdy looking man; he is lying flat, in perfect comfort, and shows neither cyanosis nor dyspnea. There is marked edema of the face, the eyelids are very much swollen, and there is a good deal of edema extending down to the jaws and to the neck. There is no edema of the legs. Externally the eyes are normal, the tongue is slightly coated, the mouth is in fair condition, and there is no enlargement of the thyroid.

The thorax is rather rounded and does not show much expansion. This is less in the lower right side, where there is dulness with absence of vocal fremitus and breath sounds. There is a corresponding area in the lower right back. These signs are regarded as being due to fluid and, in all probability, hydrothorax. There is very slight visible cardiac impulse, and on palpation very little impulse can be felt at the apex or over the body of the heart. At the base there is quite a marked shock, diastolic in time, which is interpreted as due to the forcible closure of the aortic valves. On auscultation the sounds are rather distant at the apex and over the body; the most striking point is that at the base the second sound is remarkably accentuated and has a curious musical amphoric quality. It was pointed out that this is always suggestive of dilatation of the arch of the aorta, and on palpation it is found that the arch could be readily felt in the episternal notch. The pulse is 84,

very small, and compressed with the greatest difficulty. The abdominal examination is negative and no positive evidence of ascites could be found. The liver and spleen are not enlarged.

DR. McCRAE: Mr. A, what is the most striking finding in the patient so far?

STUDENT: The edema of the face.

DR. McCRAE: Is there evidence of fluid anywhere else?

STUDENT: In the right pleural cavity and possibly also in the pericardium.

DR. McCRAE: Have you any suggestion as to the significance of the fluid in the right pleura and pericardium? Does it represent the exudate of an acute pleuritis and pericarditis, or is it a transudate?

STUDENT: Most probably the latter.

DR. McCRAE: This seems reasonable. There is no history of any acute features, such as pain or distress. If it is necessary to tap the pleura we can determine this point beyond doubt. What does the whole condition suggest?

STUDENT: It may be due to a nephritis.

DR. McCRAE: This is correct and, naturally, in view of this suggestion you wish to have a report of the examination of the urine. As he has been in the hospital for a few hours only we have no knowledge of the total daily amount and this examination is only of a single specimen. The findings are as follows: specific gravity 1.017, a moderately large amount of albumin, no sugar; microscopically, granular casts in considerable numbers. In addition, the urine contains blood.

In view of these findings the patient was questioned as to whether he had noted anything peculiar in the color of the urine. He had not done so, but evidently had not paid particular attention to this, and it is possible that it may have been present without being observed.

DR. McCRAE: Mr. B, are these findings sufficient for you to venture a diagnosis?

STUDENT: They are suggestive of acute nephritis.

DR. McCRAE: What reasons have you for this diagnosis?

STUDENT: The comparatively acute onset, the marked edema and the finding of albumin, casts, and blood in the urine.

DR. MCCRAE: I quite agree that at first glance this diagnosis is suggested, but let us look a little more into the problem before we accept it finally. Mr. C, is there anything that you would mention in this connection?

STUDENT: A point in the history is that five years ago he had an attack in which there was great swelling of the abdomen. This may have been due to nephritis.

DR. MCCRAE: This is an important item, and in the absence of any more accurate knowledge of that attack we may regard it as possibly having been nephritis. You will remember that after this he joined the army and was on active service. I should not attach any great importance to this, however, in deciding that he was perfectly sound when he entered the army. It is not always easy or even possible to diagnose nephritis on a hurried examination. It is important for us to see if we cannot get some further light on his condition. Let us observe the pulse rather more carefully. Mr. A, what is your report on it?

STUDENT: The rate is 84, the pulse is small and soft.

DR. MCCRAE: Try and see how easy it is to obliterate it.

STUDENT: It is very difficult to do so.

DR. MCCRAE: That would suggest that your description of "soft" might well be changed to the contrary. The systolic blood-pressure is found to be 220 and the diastolic 140. Mr. B, does this suggest anything as to the duration of the illness?

STUDENT: I should think that this would suggest a condition of some duration.

DR. MCCRAE: Examine the arteries carefully. In doing this, let me advise you not to restrict yourselves to the radial or the radial and brachial only. Examine all the arteries you can, not forgetting the largest and the smallest which you can ordinarily observe. You find that the femoral artery shows considerable thickening and that there are marked changes in the retinal arteries.

The diagnosis of acute nephritis does not seem so probable as it did at first glance. This is one point which I am anxious

to emphasize. We are apt to jump at the diagnosis on insufficient grounds. Sometimes, as in scarlet fever, there is no question of the occurrence of acute nephritis, but always be cautious if there is no preceding acute infection. Actually in the wards of a general hospital acute nephritis is a very rare disease, and the more carefully the patients are studied, the rarer it is. The patient will be shown again, and it may be possible then to come to a definite conclusion. Meanwhile, those of you who have made a diagnosis of acute nephritis in your minds had better put a question mark after it. There is one other point, What treatment should he had while we are studying his condition? This is not influenced by any doubt as to whether this acute attack is primary or not, for the immediate treatment is the same. The main points are as follows:

1. General Measures.—He should be at rest in bed and kept warm. The avoidance of chilling is important and care should be taken to avoid any chance of this.

2. Diet.—Milk should form the bulk of his diet for a few days. Fruit juices may be given and cocoa occasionally if he cares for it. An important point is the amount of fluid which he should be allowed to take. In this you must decide for each patient. The excretion of water may be the most difficult work which you can give the kidney to do, and large amounts may increase the edema. In this patient, from his account, the amount of urine does not seem to be greatly reduced, and we can begin by allowing him to have 1500 c.c. of fluid in the twenty-four hours.

3. Purgation.—The bowels should be freely moved, and for this he has had blue mass (0.3 gm., gr. v) followed by a saline.

4. Sweating.—This does not seem necessary in his present state, and we can safely postpone it.

5. Diuretics.—Here is an important question in the treatment. Should diuretics be given? Let me tell you what the experience of many in the profession has been. After graduation most of us are firm believers in the value of diuretics, but as the years go by a steady process of disillusionment goes on and we use them less and less. The experimental work is against diu-

retics having much value, rather the contrary, in acute nephritis, and the experience of treating patients with the disease bears this out. At present this patient is better without any diuretics in my opinion.

The patient was seen again a week later and stated that he felt greatly improved. The following points were brought out: (1) The edema of the face has disappeared entirely. (2) The signs of fluid in the right thorax are much less marked, and as the cardiac impulse is stronger, the area of dulness diminished, and the sounds heard more loudly, it is inferred that the pericardial fluid is less. (3) The eye-grounds show marked retinitis, with numerous hemorrhages, and the arteries are narrow and broadly streaked. (4) The blood count shows a moderate secondary anemia. (5) The Wassermann reaction is negative. (6) The study of the heart shows considerable hypertrophy of the left ventricle.

The urinary studies give results as follows:

Amount.—This rose from 1350 to 2350 c.c. per twenty-four hours with a fluid intake averaging 1300 to 1400 c.c. About half the amount was passed during the night, and on some occasions the night urine was larger in quantity. The total output since admission has been much greater than the intake.

Specific Gravity.—This has varied from 1.010 to 1.018, but the majority of specimens showed 1.010 to 1.012. The two-hour study showed a specific gravity of 1.010 to 1.013 except on one occasion, when it was 1.017. The night urine gave 1.012.

Albumin.—This has always been present, with a steady decrease in the amount.

Microscopic.—Hyaline and granular casts are always present in large numbers. Red blood-cells have not been found after the second day.

Functional Tests.—The phthalein test showed 20 per cent. excreted in the two-hour period. The urine urea concentration test gave 1.3 per cent.

The study of the blood shows non-protein nitrogen 52.5 mg., urea nitrogen 25.14 mg., and creatinin 1.5 mg. per 100 c.c. of blood.

DR. McCRAE: Mr. A, what opinion would you express now as to the diagnosis? Has he an acute nephritis?

STUDENT: Not in the sense of a primary attack. He has an acute exacerbation of a chronic process.

DR. McCRAE: On what do you base this opinion?

STUDENT: On the marked changes in the circulatory system, especially the arteriosclerosis and the hypertrophy of the left ventricle.

DR. McCRAE: Anything else?

STUDENT: Possibly the changes in the eye-grounds and also the character of the urine.

DR. McCRAE: What is important in the latter?

STUDENT: The low specific gravity, which varies very slightly.

DR. McCRAE: Are you willing to go any farther in your diagnosis? Could you classify the nephritis?

STUDENT: It looks like chronic interstitial nephritis.

DR. McCRAE: It does in some ways, but it is well to be cautious in diagnosing forms of nephritis. As we grow older we become more cautious. Let me suggest your reading the article on Nephritis by Dr. Henry Christian in the Oxford System of Medicine. He knows more about nephritis than most of us do. You will find that many would be content with a diagnosis of chronic diffuse nephritis in this case. The tendency is to describe the conditions present rather than to attempt a pathologic diagnosis. Thus we may say chronic nephritis with hypertension or with edema. In this patient we had both hypertension and edema at first, but now hypertension only. It may be that the edema was due to the acute exacerbation and was therefore only temporary. What will be the result of this acute attack on the kidney?

STUDENT: Probably to damage it more.

DR. McCRAE: Yes, there is little doubt of that, and in this connection let me refer you to a recent paper by Dr. C. P. Emerson (Jour. Amer. Med. Assoc., 1921, 77, 745), in which he brings out the importance of the influence of repeated slight infections and injuries from other causes on a damaged kidney. An additional observation may be noted. The patient states

that his vision is now affected, which he had not noted before. This suggests that the changes in the eye-grounds may have become much more marked during this attack.

As to the influence of the diagnosis on treatment, it is evident that the patient should receive the usual treatment for chronic nephritis. Had the condition been a primary acute nephritis we would have advised a long period of rest, hoping that there might have been recovery even after this time. Evidently this is not to be expected. The lesson to be learned is that in every case of apparent acute nephritis, unless there is a definite preceding cause, the diagnosis should be looked on with doubt. The chances are that we are dealing with an acute exacerbation of a chronic process with a much more serious prognosis.

CLINIC OF DR. ELMER H. FUNK

JEFFERSON HOSPITAL (DEPARTMENT FOR DISEASES OF THE CHEST)

CHRONIC PULMONARY TUBERCULOSIS WITH SUPRA-RENAL CORTEX SYNDROME

A. G., K2332, female, white, aged sixteen years.

Family history negative.

Personal History.—Measles in childhood and influenza at thirteen years.

Present Illness.—Patient dates onset from an attack of influenza during the epidemic of 1918. She was quite sick in bed for six weeks. After the acute symptoms had subsided she was allowed to get up and about, but slight fever and cough persisted. At times she would feel better, but was unable to gain her previous strength. She remained constantly under the care of a local physician, who by rest and addition to diet was able to increase her weight to 116 pounds in 1920. At that time her cough had almost disappeared. Several months prior to her admission to the hospital the cough returned and became productive of a small amount of yellowish sputum. Bacteriologic examination at this time revealed tubercle bacilli in the expectoration. The appetite was poor and the bowels constipated.

Upon admission to the hospital the physical examination revealed a fairly well-nourished girl of sixteen years with signs in the chest indicative of a moderately advanced pulmonary tuberculosis. There was infiltration of the right lung from the apex to the fourth rib in front and the middle of the scapula behind, and of the left lung from the apex to the second rib. There were also signs of a thickened pleura at the left base. The *x-ray* findings were confirmatory. The *sputum* examination was positive for tubercle bacilli. The *urine* examination showed nothing of note and the *Wassermann test* was negative.

Continued observation from September 22d to October 25th confirmed our provisional diagnosis of moderately advanced, active pulmonary tuberculosis. The activity is that of a low-grade, chronic lesion, the temperature varying between 99°



Fig. 163.—Note the large pendulous breasts and the area of pigmentation around the nipple. The pigmentation is more marked on the right breast than the photograph would indicate. The forearms show an abundant hairy growth. The upper lip shows a light growth of hair and the eyebrows extend across the middle line. The pubic hair is abundant and has a masculine distribution.

and 100° F. in the afternoon, the pulse-rate between 90 and 100. The weight upon admission was 112 pounds, one month later it was 114 pounds.

This patient presents, in addition, certain phenomena suggestive of an endocrine disturbance involving most likely the

cortex of the suprarenal bodies (Figs. 163, 164). First, she shows evidence of premature development, with sexual precocity; second, certain evidences of masculinity with hirsutism. At first glance she seems older than sixteen years. Her general development is that of an adult, though her height is less for her age than the average. The breasts are those of a fully



Fig. 164.—Note the excessive hairy growth over the lower legs. It extends up to the groins.

developed woman and have large pigmented areas surrounding the nipple. The breasts resemble those seen in unipara. When she speaks there is a certain harshness to her voice which she interprets as hoarseness. Her relatives have noticed it. The *laryngologic examination* by Dr. Lukens reveals no obvious lesion. Hirsutism is pronounced and masculine in distribution. The eyebrows are thick and tend to meet across the midline.

Fine hairs are present on the upper lip, and the patient has been so conscious of them as to have resorted to shaving at times. The arms, especially the forearms, the entire length of legs, especially lower legs, are covered with an abundant growth of hair. The pubic hair is abundant and of masculine distribution. The general muscular development is quite that of a strong boy rather than a girl of sixteen years.

Just what relation this endocrinopathy has to the pulmonary tuberculosis is difficult to state. One is tempted to consider their association coincidental. It is interesting to compare this syndrome with that presented in Addison's disease, in which a tuberculous lesion is known to exist frequently, either in the suprarenal body or in the chromaffin system, of which the suprarenal medulla is a part. To quote Addison's words, "there is anemia, general languor, or debility, remarkable feebleness of the heart's action, irritability of the stomach, and peculiar change of color in the skin." The syndrome presented by this patient involves not the chromaffin system, but what is known as the interrenal system. The suprarenal medulla differs in its embryogenesis from the suprarenal cortex. The functions of these two portions of the suprarenal body are distinctly different, according to our present incomplete knowledge. They are somewhat antagonistic. The active principle of the medulla is epinephrin; the active principle of the cortex is scarcely understood. Cholin has been isolated.

Among the reported cases in which the suprarenal cortex syndrome existed necropsy has revealed in some instances tumors of this structure. The polyglandular character of the endocrine disturbances gives an endless and confusing variety to the clinical pictures produced. As far as we can determine there is no gross disturbance in the functions of the other ductless glands in our patient. Bell reports an interesting example of pituitary-suprarenal syndrome in a woman who developed amenorrhea and masculine characteristics. The necropsy revealed an adenoma of the pituitary and a hyperplastic tumor of the suprarenal cortex. The amenorrhea and masculinity were the only symptoms present, and Bell infers that the suprarenal

hyperplasia was secondary to the pituitary disturbance caused by the adenomatous growth. In our patient the menses were scant, but amenorrhea was not present. The x-ray examination of the head by Dr. Manges revealed a smaller than normal sella turcica. There were no clinical evidences of pituitary disturbance as far as we could determine. Mauclaire reported last year in the French literature an interesting case in which a tumor of the suprarenal cortex was apparently responsible for the development of masculinity in a woman of thirty-eight years. The outline of the body became less rounded, the mammary glands atrophied, and a beard developed, compelling the woman to shave. These changes took place during a period of six years. Mauclaire also refers to other reported cases in which the voice becomes masculine and muscular strength develops. Suprarenal virilism and suprarenal hirsutism have been applied to this condition in women.

While I feel that we are justified in our patient in considering the probability of an endocrinopathy involving the suprarenal body, I wish to sound a caution against the too free diagnosis of suprarenal disturbances on the scant evidence which some writers suggest. Thus, with regard to hypo-adrenalism we find one writer who goes so far as to classify the patients into four types. Another writer, writing of hyper-adrenalism, claims for it an important etiologic factor in congenital pyloric stenosis, and so on. Surely we must be careful when we enter so far into the unknown fields of the endocrines not to build up a fabric of syndromes which must fall when our present conjectures are replaced in the future by the facts of scientific studies.



CLUBBING OF THE FINGERS. STAGES OF DEVELOPMENT AND ASSOCIATION WITH HYPERTROPHIC PULMONARY OSTEO-ARTHROPATHY. ETIOLOGY

THERE are a number of patients under our observation at present who show in a pronounced way the clinical manifestation known as clubbing of the fingers. In one, this phenomenon is associated with a pulmonary abscess, in another, with bronchiectasis involving the lower lobe of the left lung, and in another, with extensive pulmonary fibrosis with paroxysmal attacks of dyspnea suggesting asthma, and finally, in this patient with tuberculous pyopneumothorax. If you were to go to Dr. Jackson's Bronchoscopic Clinic this morning you would probably see there some instances of clubbing in patients with foreign bodies in the lung. The patient whom I wish to use as a text for a brief discussion of certain aspects of clubbing is a girl aged eleven years who is at present under our care for tuberculous pyopneumothorax. Her hands are illustrated in Figs. 165, 166. The appearance of the fingers is very striking and represents an advanced stage of clubbing. The distal phalanges are swollen and have a drumstick appearance. The swelling is particularly marked about the root of the nail. The overlying skin is smooth and shiny. The nail itself is rounded in both diameters. The lateral view shows the incurvation known as parrot beaked. In many patients who keep their nails cut short the parrot beaking is less marked, the nail having an appearance which has been compared to a watch-crystal. The clubbed area is cyanotic. The sluggish circulation is apparent when the slow return of the circulation is noted after slight pressure. A curious thing to be noted upon palpation is the distinctly palpable and movable root of the nail. Normally the root of the nail is attached to the periosteum. Early in the development of clubbing the nail root becomes loosened, and when palpated gives the sensation spoken of as floating.

The Development of Clubbing.—In the early stages slight curving, slight cyanosis, and mobility of the nail root occur before obvious swelling or clubbing of the distal phalanx. The change in the color of the nail has been described by Landis as an exaggerated pink closely resembling nails stained with a manicuring paste, or they may have a slight violet tinge: A very significant early change is an unusual smoothness or shininess of the skin behind the nail, *i. e.*, over the root of the nail. In many patients the lesion does not extend beyond the early stage of incurvation. I have seen it remain stationary for many years. On the other hand, it may progress rapidly to



Fig. 165.—Lateral view of clubbed fingers.

well-marked clubbing in the course of a few weeks. Some years ago there was a patient in our Children's Ward who was admitted with an empyema. He was in good health until a pneumonia six weeks before admission was followed by empyema. The fingers showed typical clubbing. He was operated upon and discharged after three weeks. The clubbing had become distinctly less at the time of discharge. Unfortunately, we were unable to follow the patient to determine if the clubbing completely disappeared. We have every reason to believe that it did. West refers to a patient with empyema in whom the clubbing became well marked in a fortnight and disappeared entirely after incision and drainage, before the end of three

months. More frequently the onset is so insidious as to be unnoticed by the patient, and once developed is persistent because of association with an incurable disease, *c. g.*, congenital heart disease, bronchiectasis, etc.

Simple clubbing of the fingers was recognized by Hippocrates, and they are sometimes referred to as Hippocratic fingers. Bamberger in 1889 and Marie in 1890 described bony changes



Fig. 166.—Clubbed fingers. No changes in the bones of forearm or hands could be detected by the x-ray.

in association with some cases of clubbing, and Marie gave this condition the name of "hypertrophic pulmonary osteo-arthropathy." Simple clubbing is a common lesion and frequently exists without the bony changes described by Marie and others. In our patient (Figs. 165, 166) most careful x-ray studies were made by Dr. Manges, who was unable to demonstrate any bony changes either in the long bones of the arms and legs or in the smaller bones of the hands and feet. Hypertrophic pulmonary

osteo-arthropathy is an uncommon lesion compared to simple clubbing. While clubbing may exist without bone changes, there is no authentic case on record in which the bone changes were noted without clubbing.

The bone changes are those of subperiosteal new bone formation in the lower ends of the radius and ulna, tibia and fibula, and to a less extent in the lower portions of the humerus and femur. Sometimes there is involvement of the small bones of the hands and feet. The bony overgrowth at the tip of the distal phalanx gives the appearance of a burr. Joint changes are slight and seldom interfere with the movements. In some instances there is a subacute synovitis.

In our patient there are no demonstrable bone changes. In a patient with a similar degree of clubbing of long duration whom I recently saw at White Haven there were striking bone changes. Perhaps the length of time in which the etiologic factor has been operating determines the development of bone changes in some cases of clubbing. The progress of the lesion is as follows: An early or incipient stage with the signs mentioned above; then the stage of distinct clubbing; and finally, the stage of clubbing plus bone changes.

Apart from the objective symptoms there is rarely any discomfort to the patient. Pain is rare. In a few cases, especially those which have developed rapidly, there is some tenderness on pressure, and in others some numbness. A marked grade of clubbing may exist without inconvenience except in the performance of the finer movements, *c. g.*, needlework, etc., etc.

The cause of clubbing is far from being clear. We know that it is usually bilateral and as such occurs in (1) congenital heart lesions and (2) chronic suppurative diseases of the lungs, of which bronchiectasis, abscess, and empyema are the most common. The unilateral cases form an interesting group and are associated with lesions causing local obstruction to the venous return from an extremity, *c. g.*, subclavian aneurysm. Instances of bilateral clubbing have also been noted upon rare occasions in a wide variety of conditions, *c. g.*, biliary and portal cirrhosis of the liver; congenital syphilis, hydatid disease and amyloid

disease of the liver (Rolleston); pyloric obstruction, cancer of the esophagus, rickets, erythremia, enterogenous cyanosis, etc., etc.

The mechanical effect of congestion has been advanced to explain the cause of clubbing in congenital heart disease and in the unilateral types due to pressure on the venous return. Subclavian aneurysm is the most frequent cause of the unilateral pressure cases recorded in the literature. In one instance of unilateral clubbing due to pressure on the right axillary artery the clubbing disappeared after ligature of the right subclavian artery (Smith's case, Trans. Path. Soc., London, 1872, xxiii, 74). In another bilateral clubbing was associated with subclavian aneurysms (Gay, Trans. Path. Soc., London, 1891, xxii, 111). In other cases a dislocated head of the humerus of four months' duration, a malignant growth in the axilla, etc., etc., were associated with unilateral clubbing.

In another group of patients a toxic factor has been advanced to explain the clubbing with or without bony changes occurring secondary to chronic infectious lesions of the lung and pleura, for example, bronchiectasis, empyema, chronic abscess, etc. Since these lesions are associated with a toxemia Marie sought to explain the clubbing and bone changes on this basis. Since there is present varying degrees of chronic peripheral congestion and cyanosis, the circulatory factor cannot be ruled out as easily in this group as the toxic factor in the first group. My own feeling is that the circulatory factor plays an equally, if not more, important part than the factor of toxemia in the cases of simple clubbing associated with bronchiectasis, etc., the toxic factor playing its greatest part in the cases with hypertrophic pulmonary osteo-arthropathy.

In a *third group* the determination of the etiology is still more obscure, for example, the clubbing in cirrhosis of the liver, congenital syphilis, polycythemia, etc. The vascular factor plus toxemia may act in the same way as in the preceding group. In at least one case of clubbing in portal cirrhosis which has been reported there was distinct evidence of bone changes characteristic of hypertrophic pulmonary osteo-arthropathy. The

difficult thing to understand is the infrequency of clubbing in the usual cases of this group.

Summary of Etiology.—The local factor in the production of clubbing is principally vascular congestion, which produces a favorable condition for the action of circulating toxins, both factors being aided by the anoxemia, which is of frequent occurrence in both suppurative respiratory lesions and congenital heart disease. In some unexplained way the etiologic factor operates to produce only clubbing in some cases and clubbing plus bone changes (Marie's syndrome) in other cases. Perhaps the element of time determines the ultimate development of the bone changes in cases which when under present observation seem to be instances only of simple clubbing.

CLINIC OF DR. HENRY K. MOHLER

JEFFERSON HOSPITAL

CASE I. RENAL GLYCOSURIA. PRESENTATION OF PATIENT

CASE II. AN INTERESTING CASE OF TUMORS IN THE NECK. DISCUSSION OF DIAGNOSIS

At previous conferences we have discussed glycosuria; the conditions with which it is associated, especially so the glycosuria which accompanies diabetes.

You will recall that by glycosuria is meant the presence of sugar in the urine as determined by the commonly used laboratory reagents, such as Fehling's, Benedict's, Haynes', and Nylander's solutions. Positive results as obtained by these tests mean that there is a reducing substance in the urine.

Question: Does it necessarily mean that because a positive Fehling test is obtained that sugar is present in the urine?

Answer: No; other substances than glucose (sugar) may give positive tests.

Question: How, then, may one be sure that the reaction is due to sugar?

Answer: By subjecting the urine to fermentation with yeast in a saccharometer.

Glycosuria may be found in other conditions than diabetes mellitus with which it is continually associated.

Physiologic glycosuria is a term applied to the presence of sugar in the urine of an individual under normal conditions. In normal individuals if delicate enough tests are used, according to Folin (Jour. Biol. Chem., 1915, xxii, p. 237), the presence of glucose may be detected in variable quantities. This, however, does not occur with the commonly used reagents.

Alimentary glycosuria is due to partaking of a meal rich in easily assimilable carbohydrate, when small quantities of sugar

may be found in the urine. The same amount of carbohydrate taken in the form of a starchy food less readily assimilable would probably not have produced glycosuria. Transient glycosuria is so called because it occurs at intervals and it disappears very promptly. Phlorizin glycosuria is glycosuria which is manifest when phlorizin is ingested. Phlorizin has the ability of robbing the body of its sugar without producing any lesion and is used experimentally.

Question: Glycosuria may be associated with disease or disorders of what glands of the body?

Answer: The pancreas, the pituitary, the thyroid, and suprarenal glands.

Yes, at times with a disturbance in the function of one or probably two, even the entire four, glycosuria may be present, and, on the other hand, increased sugar tolerance may result as a disturbance in the function of these glands.

Question: What two glands have probably most to do with glycosuria or decreased carbohydrate tolerance?

Answer: The pancreas and thyroid.

Yes, it is rather a common finding if the internal secretion of the pancreas is impaired, or if there is increased activity of the thyroid, to have a decreased carbohydrate tolerance, resulting in glycosuria.

Question: In what way do the four glands mentioned have to do with carbohydrate tolerance of the body?

Answer: In a normal individual the sugar content of the blood seems to remain at a fairly normal level except for a short time after a meal rich in carbohydrate, when it is temporarily increased until after the effects of the meal have passed off. The mechanism by which this process is adjusted is a complicated one and due to the equilibrium established by the activities of the four glands mentioned.

Question: What other forms of glycosuria exist which we have thus far not mentioned?

Answer: Those due to trauma, seen in injuries to the brain and the spinal cord, following emotional stress, renal glycosuria, glycosuria due to drugs, and diabetic glycosuria.

Yes, of the latter mentioned we have a patient before us today which seems to present evidence of the condition known as renal glycosuria.

This condition has been the subject of much controversy, and its existence has been doubted by equally as careful observers as by authorities who have described this form of glycosuria.

In the condition described as renal glycosuria or renal diabetes, as it is called at times, sugar is present in the urine with a normal or slightly subnormal blood-sugar concentration, the glycosuria and glycemia being little influenced if any by the ingestion of carbohydrate. In other words, only by studying the urine is the condition recognized, as a study of the blood discloses no abnormal findings relative to its sugar concentration. It would seem, therefore, that the kidneys are more permeable to glucose. To ascertain the points herein enumerated in an individual who subsequently falls in the group of glycosuria called renal glycosuria the blood-sugar is taken in the morning before breakfast. The percentage should be normal—0.10 to 0.12 per cent. The urine may show the presence of small quantities of sugar. The administration of a single dose of glucose with blood-sugar determination shows a rise in the blood-sugar curve such as occurs in the normal individual to 0.14 or 0.16 per cent., but returns to normal within two hours after the ingestion of the glucose. The urine during this time contains sugar.

The carbohydrate content of the diet has little effect on the sugar in the urine, and starvation likewise does not cause the sugar to disappear as readily as in a diabetic glycosuria of apparently as mild a type.

The history of the patient we have before us today with the laboratory findings are briefly as follows, and the case is presented in contrast to others we have seen mostly of the diabetic glycosuria:

CASE I

J. A. S. Case No. K2095.—Male, white, age eighteen years, has been a clerk doing office work for several years.

The patient presents himself for advice and treatment

because sugar had been found in his urine about nine months ago when he applied for admission to a fraternal order.

Family History.—Mother and father living and well. No history of renal, cardiac, or malignant disease. His paternal grandmother at the age of sixty years had her urine examined and sugar was discovered. This incident occurred in 1918, and no symptoms were associated with the glycosuria. By adjustment of the diet the sugar in the urine disappeared, and today she is in good health, and with very moderate restriction of diet the urine is kept sugar free.

Personal History.—At the age of four months the patient suffered an attack of infantile paralysis, and evidence of this condition is present now, affecting the left arm and leg. During childhood he suffered measles, mumps, scarlet fever, diphtheria, and chicken-pox. Denies venereal infection. Patient was successfully operated upon for appendicitis on November 10, 1919.

Present Trouble.—Patient has no symptoms of diabetes mellitus, or obvious symptoms of disturbance of the glands of internal secretion, and had not a specimen of his urine been requested for examination when he applied for admission to a fraternal order he probably would not have known that he had glycosuria.

Physical Examination.—Entirely negative except for slight shortening of left arm and leg, and the muscles on the left side of the body are not as well developed as in the right arm and leg, due to the attack of infantile paralysis. Reflexes diminished on the affected limbs on left side as compared with right side.

Urine examinations made while patient was in the hospital are as follows:

Quantity in 24 hours, c.c.	Specific gravity.	Albumin.	Sugar reaction.	Acetone diacetic acid.	Microscopic examination.
750	1.030	Trace	0.6+ per cent. ¹ acid	Absent	Negative
800	1.030	Trace	0.6+ per cent. ¹ alkaline	Absent	Negative
1000	1.010	Trace	Negative ² acid	Absent	Negative
900		Negative	Negative ² acid	Absent	Negative
990	1.012	Faint trace	Positive ² 0.5 per cent. acid	Absent	Negative

¹ House diet.² Starvation.³ House diet.

The patient was starved for a period of four days three months before he was admitted to the hospital, and although the percentage of sugar in his urine ranged between 1 and 2 per cent. on regular diet, the first three days of starvation (except for broth, tea, and coffee) failed to render the urine sugar free. At the end of ninety-six hours the urine of the patient was sugar free. The first day on a diet of 150 grams of 5 per cent. vegetables three times a day (a total of 22.5 grams of carbohydrate), with broth, tea, and coffee, the patient's urine was rendered sugar free. At the end of forty-eight hours, after the ingestion of a diet consisting of tea, broth, and 300 grams of 5 per cent. vegetables three times a day, a total carbohydrate intake of 45 grams for the day, sugar appeared in the urine. No blood-sugar determinations were made during this treatment. It was very obvious that we were dealing with a glycosuria that differed from those previously observed. The patient had a glycosuria unassociated with any symptoms which apparently should have readily disappeared upon several days of starvation. After the urine at the end of four days became sugar free, although a diet of 450 grams of 5 per cent. vegetables did not produce glycosuria, a diet consisting of 900 grams of 5 per cent. vegetables produced glycosuria on the second day. The patient reported one week later, having been ordered to return to regular diet, with less than 1 per cent. of sugar in a twenty-four-hour collection of urine, and at the end of a period of two weeks on regular unrestricted diet his urine was sugar free. Diet, therefore, had no consistent influence on the urine as far as its sugar content was concerned. The patient was then not seen for a period of three months, when he reported back stating that he had very markedly restricted his diet for the past three days and was willing to come into the hospital to have his case studied, as we had advised him.

Blood-sugar Determinations.—Examination by Folin-Wu method on a sample obtained before breakfast was 0.12 per cent. on the date of the first urine examination herein recorded. The morning following the last urine examination herein recorded blood-sugar was again estimated on a sample obtained

before breakfast, and found to be 0.101 per cent., following which a single dose of 100 grams of glucose was given. The blood-sugar at the end of one hour was 0.106 per cent., at the end of two hours 0.116 per cent., and at the end of three hours 0.103 per cent., with sugar present in specimens of urine examined twice during this three-hour period.

Blood Examinations.—Hemoglobin 95 per cent.; leukocytes 7400.

It would seem, therefore, that we are dealing with a patient suffering with the condition which has been described as renal glycosuria for the following reasons: It was difficult to render the patient's urine sugar free, a diet of 45 grams of carbohydrate in 5 per cent. vegetables in a twenty-four-hour period having caused sugar to reappear in the urine. One week later, on a regular diet, sugar was present in a quantity less than 1 per cent. Two weeks later, under approximately the same conditions, no sugar was present in a twenty-four-hour collection of urine. Three months later the patient, who had been on a regular diet, showed 0.6 per cent. sugar in the urine after some restrictions in the diet with a normal blood-sugar concentration. Subsequently it was observed that increasing or decreasing the diet did not necessarily cause the percentage of glucose in the urine to show a parallel increase or decrease. After an ingestion of a single dose of 100 grams of glucose the blood-sugar concentration did not rise to the maximum range found in normal individuals. The patient had glycosuria without hyperglycemia. No treatment need be instituted in a glycosuria of this type. Our patient will be instructed to report back at four-month intervals for study, or at any time if he suffers from any illness.

We are not sufficiently informed upon the etiology of this condition to state what the future of these patients will be. It is believed by some observers that the cases reported have not been under observation for a sufficient length of time to determine if they will ultimately become diabetes mellitus or not. It may be, as increased attention is focused on patients presenting these findings, our knowledge will be increased so that we will

have to modify our conception of the condition, and it will then be properly classified.

CASE II

J. B., aged twenty-three years, colored, single, laborer by occupation, admitted to the medical service of Prof. H. A. Hare because of bilateral tumors of the neck. In addition to this complaint the patient states that he has a productive cough which is worse at night. Patient has night-sweats and has lost considerable weight in the past six months.

Family History.—Mother died of pulmonary tuberculosis. Patient has no knowledge of his father, brothers, and sisters.

Personal History.—Measles is the only disease the patient can recall as having had during childhood. At the age of eight years he had an injury to his thumb, second and third fingers of left hand. No history obtainable of typhoid fever, pneumonia, pleurisy, influenza, sore throat, or rheumatism. Denies a history of niesserian or leutic infection.

Present Illness.—Patient states that six months ago the present trouble began with a spasm of the muscles in the neck on the right side which caused sufficient pain to awaken him from his sleep during the night. This spasm existed for one week, when he noticed a swelling on the right side of his neck about the size of a marble. Two days later he felt a small tumor on the left side of his neck in a location similar to that on the right side. These masses then grew steadily for two months, and for the past four months there has been no noticeable change in their size or any alteration in their consistency. Patient complained of a sore throat which lasted for three days three months ago. He complains of no pain or soreness locally and no difficulty in breathing or swallowing. His appetite is good and his bowels are regular. For the past thirteen years he has had nocturia. Cough began at the time he first noticed swelling in his neck, which was productive from the onset, and now amounts to $2\frac{1}{2}$ sputum cups in twenty-four hours. The sputum is usually blood streaked when severe paroxysms of cough occur. He denies having had a cough prior to the onset of the tumors in his neck or feeling bad in any way.

Physical Examination.—Patient is a well-nourished adult colored male. During the sixty-four days in the hospital the patient's temperature varied from normal to 103° F. Pulse varied from 90 to 130 per minute. Respirations varied from 22 to 30 per minute.



Fig. 167.—Front view of tumors in the neck.

Head.—The eyes are prominent. Pupils are equal, dilated, and react normally to light and accommodation.

Mouth.—Teeth in poor condition, tongue clean, the pharynx is injected, and the tonsils are embedded. On account of the tumors in the neck the patient is unable to open his mouth more than 1½ inches without producing considerable pain.

Neck.—Two masses situated in the lateral aspect of the neck, firm, smooth, easily moved, no nodules except for a slightly enlarged gland, about 3 cm. in diameter, located at the base and posterior to the mass on the left side. These masses are as nearly symmetric and uniform in outline as one can imagine,



Fig. 168.—Lateral view of tumors in the neck.

and are located in what appears to be identical positions on opposite sides of the neck. They seem to move very slightly on swallowing. There are no areas of softening or pulsation present. The masses are fairly freely movable and the skin overlying the masses is not inflamed and apparently not adherent. No bruits are heard. If these masses were found over the ala of the thyroid

in diameter, resembling, on examination, an enlarged lymph-node. The foregoing facts and the firmness of the tumor after six months' duration are points against the tuberculous origin of the masses.

Syphilitic Adenitis.—In the presence of a negative Wassermann test, with a denial by the patient of having contracted syphilis or gonorrhea, and no history of a primary or secondary lesion with no evidence of general adenopathy, syphilis as an etiologic factor can be almost totally disregarded. If the initial lesion were in the mouth or on the lips, the tumor on one or the other side of the neck would no doubt show a preponderance in the extent of the enlargement. The adenitis due to an initial lesion would not be of four to six months' duration. It would be rather unusual to have gummata bilateral and be more or less equal in size in a location similar to the one in which the tumors are present in this patient. Further evidence against a gumma is the fact that a gumma of six months' duration would show breaking down of the tissues. It would, therefore, seem that we can safely rule out syphilis as the etiologic factor.

Tumors of the Carotid Gland.—The findings common to tumors of the carotid gland and to the tumors present in our patient are the location, the contour, which is smooth, and the tumors are single. Carotid gland tumors are not tender and the deformity is the chief complaint. Evidence which negatives the diagnosis of tumors of the carotid body are the absence of transmitted pulsation, bruit, and thrill. The movement of the tumors in this patient while restricted in range are not restricted in direction, in contradistinction to tumors of the carotid gland, which can be moved laterally, but not vertically.

Hodgkin's Disease.—This disease usually begins in the lymph-nodes of the neck, although it may begin in the lymph-nodes anywhere in the body, manifesting itself by causing an enlargement of these nodes, especially those of the posterior triangle. Males are affected more frequently than females, and although the disease can attack persons of any age, it is more common under the age of thirty years. Following the enlargement of the nodes of the neck the nodes in the axilla or the

groin of the same side show evidence of enlargement. The disease is usually more advanced on one side of the body than the other. Less commonly the enlargement remains stationary for some time in a group of nodes before the process becomes manifest in distant nodes.

Several regions may be involved simultaneously, but as a general rule, if the nodes of the neck are the first to be involved, weeks or even months may elapse before the other side becomes involved. Early the nodes are firm and not adherent and retain their outline, with the skin overlying not becoming adherent. Later the nodes may form large masses by the welding together of their capsules. This tumor mass is usually surrounded by a capsule of its own which may give the palpating finger the impression of a globular or oval tumor. The points in the history of this patient in favor of the diagnosis of Hodgkin's disease are that the patient was apparently a healthy individual when these tumors became evident. Tuberculosis of the lungs and Hodgkin's disease are often associated. The tumors began as small, firm, discrete and freely movable masses, coalesced early, later to form large bilateral masses, which for the past four months have not increased in size. Against the diagnosis is that it is not common to find lesions in Hodgkin's disease remaining localized for a period of six months, usually having attained the size of the present tumors, other glands in the body are involved. Although the x-ray examination of the chest shows that some enlargement of the intrathoracic glands is present, this enlargement is no more so than one would expect to be associated with the tuberculous pulmonary lesion.

Enlarged Lateral Lobes of Thyroid.—The tumors are situated too far from the median line of the neck, do not move up and down upon the act of swallowing, and the thyroid gland is distinctly palpable though not enlarged. No evidences of hyperthyroidism are present. The masses are smooth and have no appearance of being a bilateral cystic goiter.

Bilateral aneurysm of the carotid arteries is uncommon. No expansile pulsation or bruit are present in these tumors, which eliminates the possibility of aneurysm.

Lymphadenoma or Lymphosarcoma.—These conditions are progressive in character, involving group after group of glands, and evidences of metastasis are present usually before a period of six months elapses. The cutaneous veins overlying the tumors become enlarged and tortuous and pain is usually an early and prominent symptom. It is not uncommon to have inflammatory changes present. In view of the absence of these findings it seems one is justified in eliminating the consideration of lymphadenoma and lymphosarcoma as a diagnosis of the condition with which we are dealing.

Adenitis from infection of adjacent structures, such as teeth, tonsils, sinuses, is a cause of tumors in the neck. It is not likely that the condition would remain stationary for four months in the absence of the removal of the cause. There is also no evidence of softening or suppuration and no tenderness of the masses. In favor of a diagnosis of an inflammatory adenitis, however, is the poor oral hygiene and the diseased condition of his teeth.

As previously stated, with a six months' history of the existence of the tumors without suppuration and no changes in the size for four months is evidence against the diagnosis of simple adenitis. Leukemia can be ruled out by the absence of a typical blood-picture.

The evidence obtained in reviewing the possibilities suggest that the tumors are either tuberculous glands which have formed a capsule of their own or Hodgkin's disease. Considering all the evidence it would appear that a diagnosis of Hodgkin's disease is warranted.

The finality of this statement must be dependent upon the pathologic diagnosis of the tissue removed.

Professor J. Chalmers DaCosta, after examining these masses, expressed the opinion that clinically he considered the condition Hodgkin's disease, and advised that Dr. Thomas Shallow remove the tumors under local anesthesia, allowing an interval of three weeks to elapse before the second tumor was removed. Following his advice the operations were performed. The wounds healed promptly by primary union.

The following is a brief of the report submitted by Dr. B. L. Crawford, pathologist, on the tumors removed by Dr. Shallow:

Bacteriology.—No acid-fast bacillus was demonstrable in spreads prepared from fresh tissue, nor in tissue stained with carbolfuchsin.

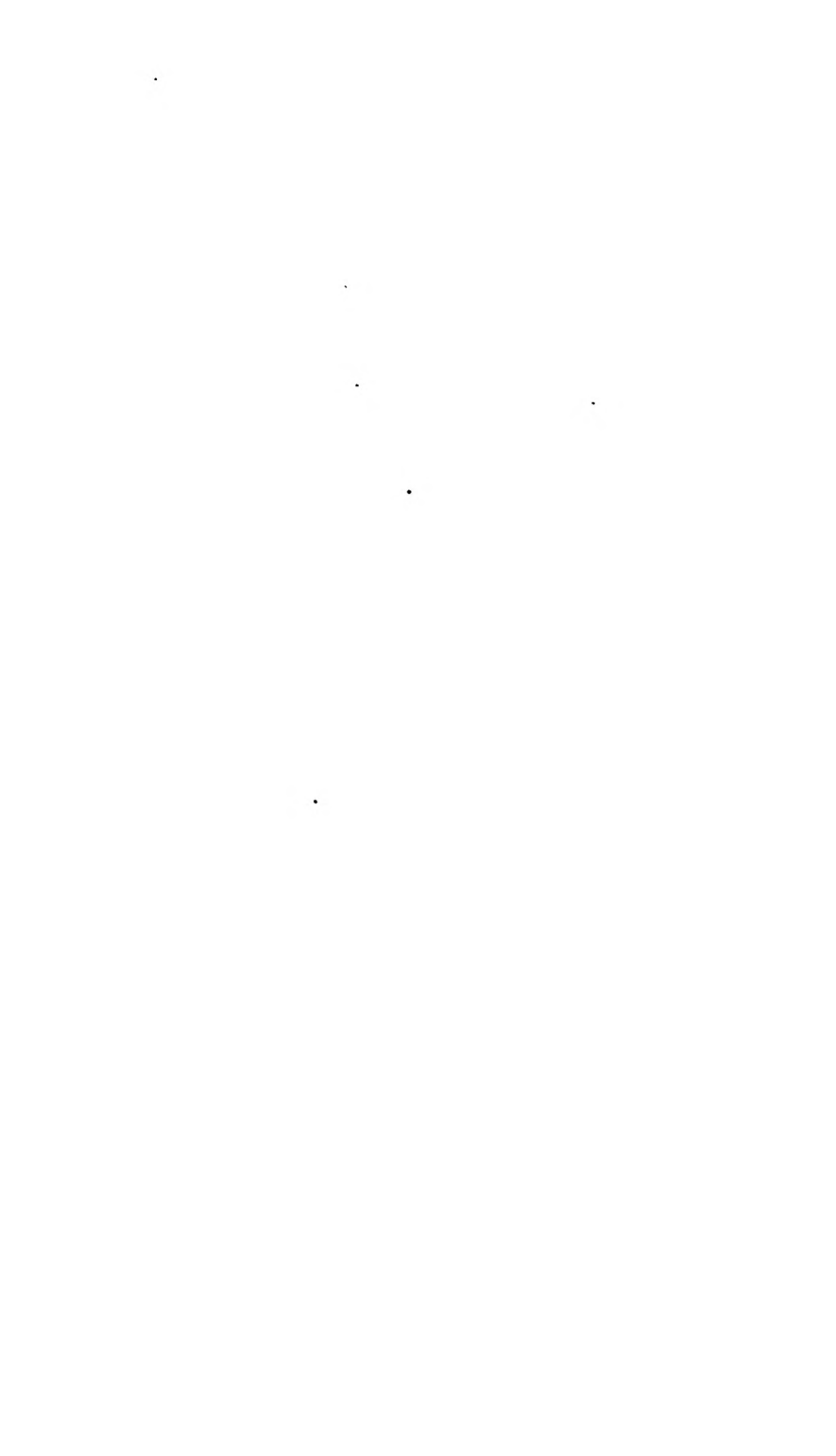
June 23, 1921: Guinea-pig injected in left groin, subcutaneously, with material from nodes.

August 16, 1921: Two enlarged nodes were removed from left groin of guinea-pig at point of injection. They contained numerous yellowish foci about the size of a millet seed, and in the center were necrotic and caseous. No tubercle bacillus demonstrable.

Histology.—Sections of the glands are encapsulated, and at the margin small follicles resembling those of a lymph-node are observed; the remainder of the tissue is composed of large necrotic areas and very cellular collections with a fine connective-tissue reticulum. Small foci of mononuclear leukocytes are present in the sections, but no giant-cell could be detected.

While no acid-fast bacillus could be demonstrated in the smears or stained sections, histologically the lesion is believed to be tuberculous. In some places the cellular areas resemble Hodgkin's disease, but the cytology is not typical.

Diagnosis.—Chronic fibrocaseous tuberculous lymphadenitis.



CLINIC OF DR. EDWARD WEISS

FROM THE DEPARTMENT OF PATHOLOGY, JEFFERSON MEDICAL COLLEGE

THE UREA CONCENTRATION TEST FOR KIDNEY FUNCTION

For many years the diagnosis of kidney disease depended largely, aside from the clinical findings, upon the result of urinalysis. But in more recent times it has been found that this is not as reliable a guide as formerly was thought. Many observers now believe that albuminuria and even casts do not in themselves mean kidney disease, and, on the other hand, the absence of albumin and casts from the urine does not exclude the possibility of a renal lesion. The further fact that the degree of albuminuria bears little relation to the severity of the disease has made it necessary to formulate more accurate methods to aid in the diagnosis and prognosis of a renal lesion. These may be outlined as follows:¹

1. The determination of the rate of excretion of a known amount of a chemical substance, injected or ingested. Of these methods the phenolsulphonephthalein test is most generally used.
2. The determination of the degree of retention in the blood of various metabolic products, such as urea, non-protein nitrogen, creatinin, and uric acid.
3. The comparison in a patient on a known test diet of the ingestion and excretion of nitrogen, salt, water, etc., often spoken of as the "two-hour" test.
4. A determination of the ratio between the concentration of various metabolic products, ordinarily urea, in the blood, and their excretion in the urine, the result being expressed as a ratio of excretion or coefficient. This is known as Ambard's coefficient or McLean's index.

Of the first methods, the phenolsulphonephthalein test is the one most generally used, and for this reason it is unnecessary to dwell upon the manner in which it is performed. One word of caution may be mentioned, however, and that is the accuracy of the syringe used in the injection of the dye substance; syringes often vary from 10 to 20 per cent., and this has a great influence upon the total excretion of the minute amount of dye substance used in the test. Another technical objection is the method of administration; nearly all patients object less to a dose of medicine by mouth than an intramuscular injection.

Aside from these technical matters many observers are convinced that the phenolsulphonephthalein test is of but little value in the early stages of chronic nephritis. Addis and Watanabe² in their work on the urea-excreting function of the kidney object on the well-established ground that the pathologic process in early or moderately advanced chronic nephritis is, as a rule, not uniformly distributed, but involves certain areas of the kidneys more than others, and commonly leaves parts entirely unaffected, so that the slightly or wholly unaffected sections of the kidney may find no difficulty in excreting this minute amount of dye in a manner entirely comparable to the mode of excretion of normal kidneys.

The last objection holds true for the value of the determination of the degree of retention of such metabolic products as urea in the blood. Not until the kidney is grossly diseased (some authors state that the quantitative reduction must be to one-fourth of its normal anatomic structure) do the nitrogen constituents increase in the blood. This detracts from the value of the determination in the diagnosis of an early or moderately advanced renal lesion. The further fact that the degree of nitrogen retention is greatly influenced by the previous diet often makes the test difficult to interpret. Then, too, these are methods demanding excellent laboratory facilities and considerable skill in performance, and for these reasons are inaccessible to the average practitioner.

The administration of a test diet and the determination of the excretion of nitrogen, salt and water, or the "two-hour"

test, as some prefer to call it, may be modified for ordinary purposes in the following manner: Permit the patient to have three full meals; all the water desired with meals, but no food or fluids between. The urine is collected in two-hour periods during the day and one specimen for the total night elimination—all are measured and their specific gravities taken. The normal individual should show a polyuric response to meals, should vary the specific gravities of any two specimens by at least 9 points, and the night urine should be small in amount (ordinarily less than 750 c.c.) and high in specific gravity (1018 or above). A departure from the normal is noted in a failure of concentrating power and a loss of kidney elasticity, *i. e.*, there is a tendency toward a large amount of night urine of low specific gravity and later a fixation in quantity and specific gravity of the day specimens.

Though the test in this form may be generally applied and undoubtedly gives splendid results, it has been found so delicate that its interpretation is often difficult and sometimes hazardous. Thus it is not only in chronic nephritis that the response to a test-meal may be altered, but likewise in pyelitis, cystitis, hypertrophied prostate, marked anemias, pyelonephritis, polycystic kidney, and diabetes insipidus.³ The state of the water reserve of the tissues is another factor of considerable importance in affecting the response to a test-meal. It is obvious that an edematous patient will react differently to the ingestion of fluids and diuretic substances than a normal person or a non-edematous nephritic. This makes the correct interpretation of the test exceedingly difficult.

The last method mentioned, known as Ambard's coefficient or McLean's index, may be dealt with very shortly. The procedure is so highly technical as to be impossible of performance outside of hospital practice, and is so laborious that the patient may refuse to be utilized. Again, it is influenced by extrarenal factors, and lastly, it is not so certain that it gives very much more information than the determination of the degree of nitrogen retention.

Though it is well understood that no one test can be thor-

oughly satisfactory, still one is justified in searching for a method of testing renal function which will show earlier involvement than the phenolsulphonephthalein test or the determination of the degree of nitrogen retention; which will be easier to interpret than the "two-hour" test; and not so technical as the methods of Ambard and McLean. For reasons about to be enumerated a method employing administered urea as a test substance would seem to be best adapted to overcome the objections so far raised.

Urea as a Test Substance for Kidney Function.—Urea possesses certain advantages as test substance for renal function, which may be outlined as follows:

1. It is a true end-product of protein metabolism and is incapable of further alteration within the body.

2. It is a normal excretory product.

3. It is excreted practically only by the kidney.

4. It may be given in large doses and is readily absorbed and taken up equally by all the fluids and tissues without producing any ill effects. Only when given in immense doses—100 to 125 gm.—does it produce symptoms of intoxication.

5. The administration of a large dose of urea throws a strain upon the kidneys. This appears to be its greatest advantage as a test substance for renal function. As before mentioned, the lesion of early or moderately advanced chronic nephritis is a patchy one, and the areas of normal or little involved kidney substance apparently have no difficulty in eliminating a minute amount of a dye, such as phenolsulphonephthalein, but it is felt that such kidneys will show functional incapacity when subjected to the strain of a large dose of urea. As an example we are well aware that a diseased heart is not necessarily a decompensating heart and may meet perfectly readily the ordinary demands of circulatory function. When there is a sudden circulatory demand, however, the cardiac mechanism proves inadequate and the symptoms and signs of decompensation become apparent. In the same manner a diseased kidney may meet the ordinary functional demands and the lesion remains latent. When a strain is put upon the kidney, however,

the reserve power being lessened, it fails to meet its demands and shows functional inefficiency. Thus the administration of a large dose of urea should bring to light latent kidney deficiencies.

The Urea Concentration Test.—MacLean and DeWesselow⁴ have formulated a test with administered urea depending upon the decreased concentrating power of a diseased kidney. Their technic has been but slightly altered in the following work:

One cup of coffee and two slices of toast are permitted for breakfast and thereafter food and fluids are restricted until the completion of the test. About an hour and a half after breakfast the patient voids, and then takes by mouth 15 gm. of urea dissolved in 100 c.c. of water (flavored with tincture of orange).^{*} The patient passes urine at the end of one hour and at the end of two hours, the second hour specimen being saved for analysis, the first being measured, however, to note any diuretic effects. The administration of urea induces a diuresis in a few individuals and in cases showing an excretion of from 350 to 600 c.c. or more in two hours any tendency to a low concentration, in the absence of other signs of renal disease, may be put down to excessive fluid. In such cases, however, a third hour specimen may be saved and analyzed. Urea is estimated by the urease method, but may be determined by the ordinary hypobromite method which, though somewhat inaccurate, gives approximately correct results.[†] A urea concentration in the second hour specimen exceeding 2 per cent., *i. e.*, 2 gm. of urea to the 100 c.c. of urine, indicates a fairly efficient kidney, and less than 2 per cent. an inefficient kidney—the lower the concentration, the more serious the kidney damage.

From more than one hundred such determinations com-

^{*} If blood is to be drawn for urea determination it must be taken before urea administration, for it has been found that the administration of 15 gm. of urea raises the blood urea level from 8 to 20 or more mg. per 100 c.c. within two hours, and it may remain so for twenty-four hours or more.

[†] The original authors of the test used a modified hypobromite method, and found it very satisfactory. In my preliminary work⁵ the ordinary hypobromite method was used together with the more accurate urease method, and was found to give approximately correct results.

TABLE I
THE "UREA CONCENTRATION TEST" COMPARED WITH OTHER FUNCTIONAL METHODS IN THE STUDY OF RENAL DISEASE

Case.	Name.	Age.	Sex.	Clinical diagnosis.	Blood-pressure.	Eye-grounds.	Urinanalysis.			Blood urea.	Phthalic acid, two hour, per cent.	Urea concentration.	Comment.
							Specific gravity.	Alb.-min.	Casts.				
24	D. M.	24	M.	Normal	120		1020			15	68	2.9	
26	D. S.	25	M.	Normal	108		1018			17	50	2.7	
10	J. H.	50	M.	Chronic nephritis	160	Neg.	1012	Trace	Hyaline	18	75	1.3	
22	F. P.	42	M.	Chronic nephritis	200	Pale disk; cont. vessels	1015	Trace	Granular	26	60	1.6	
20	N. G.	35	M.	Chronic nephritis	130	Neg.	1015	Cloud	Hyaline	17	50	1.8	
15	M. R.	40	M.	Chronic nephritis	140	Neg.	1020	Trace	Hyaline	13	50	1.75	
13	E. N.	34	F.	Chronic nephritis	110	Neg.	1010	Trace	Hyaline	16	45	1.9	Death; uremia.*
66	R. W.	57	M.	Chronic nephritis	230	Optic neuritis	1015	Trace	Hyaline; granular	22	40	1.7	Test-meal; fixation of specific gravity.
11	M. G.	42	M.	Chronic nephritis	208	Retinitis	1015	Cloud	Hyaline; granular	18	40	1.0	Death; apoplexy.
29	E. P.	60	M.	Chronic nephritis	210	Disk marg. hazy	1008	Trace		32	35	1.6	Test-meal; no fixation.
9	P. H.	63	M.	Chronic nephritis	160		1010	Trace	Hyaline	27	30	1.3	
25	H. E.	58	F.	Chronic nephritis	170		1006	Trace		17	25	1.3	
44	E. O'B.	33	F.	Chronic nephritis	180		1010	Trace	Granular	38	25	1.3	
72	W. M.	29	M.	Chronic nephritis	220	Arteries cont. and tort.	1010	Cloud	Blood	33	20	0.7	
23	F. K.	49	M.	Chronic nephritis	230		1004	Trace	Hyaline; granular	38	17	0.9	Death; uremia.
14	R. B.	29	M.	Chronic nephritis	220	Retinitis; hemorrhage	1009	Trace	Hyaline; granular	76	10	0.9	
8	V. S.	54	M.	Chronic nephritis	210	Retinitis	1014	Trace	Hyaline; granular	76	10	0.9	
21	B. O'D.	53	F.	Chronic nephritis	200	Retinitis	1002	Trace	Hyaline	40	5	0.9	
16	A. W.	40	F.	Chronic nephritis	236		1010	Trace	Hyaline	97	Traces	0.8	Death; uremia.
7	W. M.	30	M.	Chronic nephritis	160	Neg.	1010	Trace	Hyaline; granular	121	Traces	0.8	
57	J. M.	37	M.	Chronic nephritis	220	Albuminuric retinitis	1010	Cloud	Hyaline; granular	162	Traces	0.9	Death; uremia. ¹ Test-meal; marked fixation.

* Necropsy.

pared with other methods of estimating renal function the cases recorded in the tables shown on pages 920, 922, and 925 are selected as representative of the various types of renal and cardiovascular disease encountered.

In Table I are recorded selected cases of chronic nephritis with hypertension, *i. e.*, the variety usually spoken of as chronic interstitial nephritis. At the top of the table are placed for the sake of comparison two normal reactions, showing blood urea and phenolsulphonephthalein figures within normal limits and urea concentrations exceeding 2 per cent. Cases of mild chronic nephritis are next in order, and show, in spite of normal urea and phenolsulphonephthalein figures, an inability to concentrate to 2 per cent. Moderately severe chronic nephritis (Cases 25 and 44), with phenolsulphonephthalein outputs of 25 per cent., concentrate urea to but 1.3 per cent.; and severe chronic nephritis (Cases 16, 7, and 57), with a high degree of nitrogen retention, and only traces of phenolsulphonephthalein elimination, fail to concentrate to 1 per cent. Thus it is seen that the results of the urea concentration test, the phenolsulphonephthalein elimination, and the degree of nitrogen retention are closely approximate in the moderately advanced and severe cases of chronic nephritis, but that in some of the milder cases it is the urea concentration test which indicates the functional deficiency. I wish to emphasize at this point the use of the latter term. Since it is impossible by means of functional methods to visualize the amount of structural damage to the kidney, one is justified only in interpreting the results of these methods upon a physiologic basis, and stating not that the kidneys are normal or diseased, but rather that they are efficient or inefficient.

The Urea Concentration Test in Cardiovascular Disease.—There are occasional cases of cardiovascular-renal disease in which it is desirable to know to what degree the kidneys are responsible for the clinical picture. Many of these patients show marked albuminuria and a considerable number of casts and often a marked edema.

From a number of such cases 2 are selected in Table II

TABLE II
THE "UREA CONCENTRATION TEST" IN PASSIVE CONGESTION OF THE KIDNEYS

Case.	Name.	Age.	Sex.	Clinical diag- nosis.	Blood- pressure.	Eye- grounds.	Urinalysis.			Blood analysis.			Phthal- ein, two hour, per cent.	Urea concen- tration.	Comment.
							Sp. gr.	Albu- min.	Casts.	Two-hour test.	Urea.	N.P.N.	Creat- inin.		
36	I. A.	45	M.	Pulmonary emphyse- ma; chronic myocarditis	120/70	Low- grade optic neuritis	1025	Cloud	Hyaline; granu- lar		23	47	1.8	3.6	Marked dyspnea and cya- nosis. Death.* Edema.
53	J. R.	65	M.	Aortic regur- gitation	120/70	Neg.	1025	Trace	Granu- lar	Fixation of quan- tity and specific gravity	24	53	2.4	2.8	
										No fixa- tion	18	40	2.0	3.0	No edema.

Showing the influence of the water reserve of the tissues on the test-meal response.

* Necropsy.

which show the value of the urea concentration test as an aid in differential diagnosis. Case 36, an adult white male with marked dyspnea and cyanosis, edema and albuminuria, and all the clinical evidences of renal involvement, showed a urea concentration of 3.6 per cent. At necropsy there was pulmonary emphysema, chronic peribronchial lymphadenitis, and a confirmation of the renal functional finding in that the kidneys showed only passive congestion—no gross anatomic alteration.

Case 53, one of cardiac decompensation in whom there was a question as to the degree of renal involvement, showed during the period of edema a fixation of quantity and specific gravity in the two-hour test, a slight degree of nitrogen retention, and a low excretion of phenolsulphonephthalein—25 per cent. After the disappearance of his edema the test-meal response was normal, the retention figures were slightly lowered, and the phenolsulphonephthalein excretion was 50 per cent. Both before and after the disappearance of his edema the urea concentration was well above 2 per cent., indicating the value of the test in a type of case in which the degree of water reserve of the tissues profoundly alters the test-meal response and the phenolsulphonephthalein excretion. The failure of the latter test in these cases is probably a problem of absorption and would not occur if the dye was given intravenously. That the factor of absorption from the gastro-intestinal tract enters into the accuracy of the urea concentration test is likewise true, and it is for this reason that the urea had best be given on an empty stomach and the analysis made on the second hour specimen (to permit complete absorption of the drug).

Value in Prognosis.—In those cases showing a progressive lesion the test demonstrated the downward course of the disease. Thus Case 13 (Table I), a chronic nephritis with an acute exacerbation following ether anesthesia, showed an initial concentration of 1.9 per cent. Ten days later—one week before the death of the patient—she concentrated to but 1.5 per cent. A partial necropsy was obtained, at which the kidney was found to show a recently engrafted glomerulobular lesion on a chronic interstitial nephritis.

Case 29 (Table I), a slowly progressive chronic interstitial nephritis, showed on admission a phenolsulphonephthalein excretion of 35 per cent., a blood urea of 32, and a urea concentration of 1.6 per cent. He improved with rest and was discharged from the hospital, only to return three months later complaining of severe dyspnea. At this time his phenolsulphonephthalein and urea retention figures were about the same as on admission, but his urea concentration was reduced to 1.4 per cent., indicating the delicacy of the test as an aid to prognosis.

On the other hand, a case of mercuric chlorid poisoning, to be reported elsewhere,⁶ showed a progressive rise of urea concentration from 0.85 per cent. (July 27, 1920) to 1.85 per cent. (September 15, 1920), the date of the patient's discharge, clinically cured. This progressive rise of concentration power closely paralleled the phenolsulphonephthalein excretion and curve of blood urea. The patient returned three months after his discharge from the hospital, and at that time showed a blood urea of 15 mg. per 100 c.c., a phenolsulphonephthalein elimination of 60 per cent. in two hours, and a urea concentration of 2.6 per cent.; demonstrating the return to a physiologic normal in the acute nephropathies of this nature.

Limitations of the Urea Concentration Test.—The normal kidney behaves differently toward the various substances of excretion, and should be judged separately for each. This difference in behavior becomes even more marked in renal disease; in the type commonly known as chronic interstitial nephritis there is usually a tendency to nitrogen retention, while in the form spoken of as chronic parenchymatous nephritis salt and water are, as a rule, eliminated with difficulty. It is in the latter type of case that functional methods generally are inadequate, and the urea concentration test, as may be noted in the column so headed (Table III), likewise fails to indicate the degree of functional impairment. It must be stated, too, that in certain other cases of mixed chronic nephritis (nitrogen, and salt and water retention) the test, in spite of distinct clinical and functional evidences of nephritis, at times fails to demonstrate the renal inefficiency.

Conclusions.—The urea concentration test appears to be a simple and fairly reliable method of determining the efficiency of the kidney, but, notwithstanding certain theoretic advantages which it possesses over other methods, practically it is not ideal, and should, therefore, be considered a useful adjunct test to be employed in conjunction with other methods, the whole being weighed with the clinical data in an evaluation of a case of renal disease.

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CONTRIBUTION BY DR. E. B. KRUMBHAAR

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PITUITARY DISORDERS IN THEIR RELATION TO ACROMEGALY (HYPER-PRE-PITUITARISM), WITH SUGGESTIONS FOR THE USE OF A MORE PRECISE TERMINOLOGY

DISEASES of the pituitary gland possess a peculiar interest not only for the internist, ophthalmologist, and neurologist, on account of the character of the symptoms produced, and for the surgeon on account of the problems of operative intervention, but also to the physiologist and "dynamic pathologist" concerned with the relation of this structure to general body functions in health and disease. In fact, our present knowledge of the pituitary has perhaps been chiefly advanced by the clinical study of cases of disordered function, a belief which has made me think it worth while to present the accompanying series of cases. Since the appearance of Cushing's masterly monograph ten years ago but little practical progress has been made, so that we have not yet fulfilled his prophecy that "we are unquestionably approaching a stage in our knowledge when the classification or grouping of the cases here employed as a provisional basis for clinical use will no longer be necessary." For instance, in the most recent consideration of this topic¹ the pituitary is not once considered as other than a single gland, a failure that would be much less apt to occur if a more precise terminology were in vogue. Before discussing cases in detail, therefore, I would like to make a plea for the use of more specific terms that we have found useful in our discussions in these laboratories.

¹ Hutinel, V. Maillet, *Dystrophies Glandulaires et Mono Symptomatiques*, *Annales de Med.*, 1921, x, 100.

The pars intermedia and the pars neuralis are, though anatomically distinct, considered with propriety from a functional point of view as the "posterior lobe." It is therefore obvious that disturbances of pituitary function may be grouped under five heads: (1) overfunction of the anterior lobe; (2) underfunction of the anterior lobe; (3) overfunction of the posterior lobe; (4) underfunction of the posterior lobe; (5) perverted function of one or both lobes. In spite of this obvious state of affairs, it is still customary (perhaps on account of the unavoidable length of more precise terms) to disregard the mutual independence of the two lobes and use the older terms hyper-, hypo-, and dyspituitarism. This lack of precision places such a handicap on the intelligent discussion of the nature of disorders of pituitary function and of given endocrine cases that I venture to recommend the use of more precise, though clumsier terms. If "hypophysis" and "pituitary" were not so firmly established as synonymous, one might take advantage of their etymologic derivations to designate the first two classes as hyper- and hypopituitarism, and the next two, as hyper- and hypohypophysism, disregarding the fact that the pars intermedia probably has an ectodermal origin.

With the addition of an extra syllable, however, we may use: (1) hyper-pre-pituitarism, (2) hypo-pre-pituitarism, (3) hyper-post-pituitarism, (4) hypo-post-pituitarism, (5) dyspituitarism.

1. As hyper-pre-pituitarism are considered such growth changes as giantism and acromegaly, which are commonly associated with hyperplasia or adenoma of the acidophil cells of the anterior lobe.

2. Hypo-post-pituitarism is manifested, in the present state of our knowledge at least, by dwarfism. There are but few definite clinical observations to support this view, but it is probable this deficiency is a factor in many cases of dwarfism. The possibility of such a lesion is well demonstrated by a recent finding in these laboratories of almost complete loss of the anterior lobe (see Fig. 186).

3. Hyper-post-pituitarism is likewise a rather hazily understood condition. Lessened sugar tolerance, increased basal

metabolism, and other antitheses of the fourth class might logically be included here, and, in fact, have been so placed in a few instances.

4. Hypo-post-pituitarism includes a large and better known group of disorders, such as are prominent in Fröhlich's syndrome and similar disturbances of metabolism, cardiorenal vascular regulation, and sexual characteristics.

5. Under dyspituitarism should be grouped, following Cushing's suggestion, mixed or transition cases, *i. e.*, any perversions of the functions already referred to or those cases which have not shown a preponderance of symptoms attributable to any one lobe. Here also must be placed cases that have progressed from one of the first four groups to a composite mixture of symptoms referable to hyper- or hypofunction of both lobes, as Cushing has demonstrated to be so frequently the case in acromegaly. In using such terminology it must also be borne in mind that the relation of certain clinical factors of considerable importance, such as "neighborhood" or distant cerebral symptoms and of the other glands of internal secretion, have been left out of consideration.

To return to the relation of pituitary tumors to acromegaly, let it suffice here to recall a few prominent landmarks: 1. Their frequent association, which was firmly established by clinicopathologic evidence within a few years of Marie's¹ original description of this striking clinical condition in 1886. 2. Massalongo's² and Tamburini's³ hypothesis that acromegaly is due to a hyperfunction of the anterior lobe (hyper-pituitarism); with Massalongo's corollary that giantism results if the epiphyses are not yet ossified, this is now the most widely accepted view. 3. Benda's⁴ demonstration that increase of the acidophil cells of the anterior lobe was probably the important factor in producing hyperfunction. 4. The discovery of various accessory hypophyses: (a) Hypophysis accessoria cranii; (b)

¹ Marie, P., *Revue de Med.*, 1886, vi, 297.

² Massalongo, R., *Riforma Med.*, 1892, viii, 74, 871.

³ Tamburini, A., *Riv. Sper. di freniat*, 1894, xx, 559.

⁴ Benda, C., *Berl. Klin. Woch.*, 1900, xxxvii, 1205.

H. a. canalis craniopharyngea; (c) H. a. pharyngea. 5. And Erdheim's¹ demonstration of an acromegalic with a normal hypophysis, but with acidophil adenoma of the pharyngeal hypophysis. The arguments for and against the hyperfunction conception of acromegaly are to be found in Cushing's book (page 250 *et seq.*). In view of Erdheim's discovery, however, it seems only proper to throw out of count all cases of acromegaly with normal pituitaries in which the accessory hypophysis have not also been most carefully studied. In cases of acromegaly with non-acidophilic tumors of the pituitary the possibility of a progression beyond the acidophil stage must also be borne in mind. Even when many of the so-called exceptions to the hyperpituitarism theory are put in the suspicious class by such means, however, it must be recognized that other valid exceptions still exist, and will probably increase in number. Bailey² has recently supported this view with the cases of Cagnetto, Zak, Krauss, and others (acidophilic increase without acromegaly), and with Yamada's case of acromegaly without pathologic change in the pituitary. I cannot see, however, that adequate evidence has been produced to support the view that the hyperplasia when present is secondary to some biochemic disturbance.

Case I. (Phila. Gen. Hosp., Autopsy No. 5645.) Chronic Acromegaly. No Other Signs or Symptoms of Cranial Disturbance. Death from Tuberculous Pericarditis and Cardiac Failure. At Autopsy, Acidophil Adenoma of Anterior Lobe of Pituitary.—*History*.—John Davis, negro, aged forty-three, laborer, admitted to the service of Dr. Riesman and Dr. Norris in the Philadelphia General Hospital on October 25, 1920, suffering from shortness of breath and other signs of marked cardiac decompensation.

The diagnosis of acromegaly was made by one of the staff, as he saw the patient arrive in a taxicab. No change in his appearance, noticeable either to himself or his friends, had occurred in at least the past twenty-one years. Photographs

¹ Erdheim, J., *Franf. Zeitsch. of Pathol.*, 1910, iv, 70.

² Bailey, P., *Jour. Med. Research*, 1921, xlii, 349.

or details of size of hands and feet were, unfortunately, not available.

For three months he had been suffering from shortness of breath on exertion and evening edema of ankles and feet. Before that time he had successfully labored in a meat packing establishment carrying heavy cases of ice and boxes. He was usually called on to do the hardest lifting on account of his great strength. Three months before admission he weighed 248 pounds.

Except for gonorrhea at eighteen and a chancre at twenty-three, he had always been healthy and strong, and had never



Fig. 169.—Case I. Showing large jaw and prominent soft tissues of nose and mouth.

taken a dose of medicine until his present illness. Was never married. Was a heavy whisky drinker and user of tobacco.

His father, who died at sixty-three of heart trouble, was said to have been a very large man and to have had a large head and hands. Other family history negative.

Examination shows a middle-aged colored "giant" (as he was 5 feet, 9 inches tall, this must have referred to his great muscular development). Head "diamond" shaped, greatest circumference 25 inches. Occipitontal 12 inches, occipitofrontal 10 inches. Face covered with short, kinky, gray-black hair; hair normal; eyeballs prominent. Pupils and eyesight normal.

Tongue very large. Teeth in fair condition, spacing between teeth of upper row. Heart dulness increased, action arrhythmic, with mitral systolic murmur, weak muscle sounds, and roughened second aortic. Lungs: signs masked by loud bubbling râles. Death from pulmonary edema.

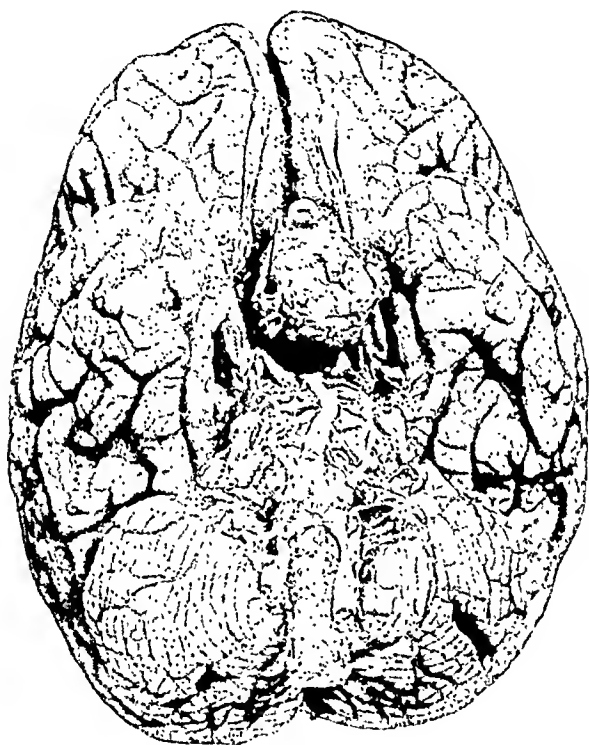


Fig. 170.—Case I. Base of brain showing adenoma of pituitary.

Clinical Diagnosis.—Acromegaly, acute myocarditis with decompensation, pulmonary edema.

Autopsy (Drs. B. Crawford and N. Winkleman).—Skull unusually thick, especially in the frontal and occipital region, in one area measuring 2 cm. in diameter. The dura is normal; the pia only slightly injected and presents no peculiarities.

The brain itself is of fairly good size and weighs 1350 grams. It is not edematous. On removal of the brain it is noted that there is a large tumor of the pituitary region which pulls the optic nerves taut, and when this tumor is lifted up with the pituitary the fossa is found to be very much deepened and widened, and the tumor adherent to the surrounding periosteum and difficult to separate from it. At the anterior angle of the tumor a part of the mass has broken through the

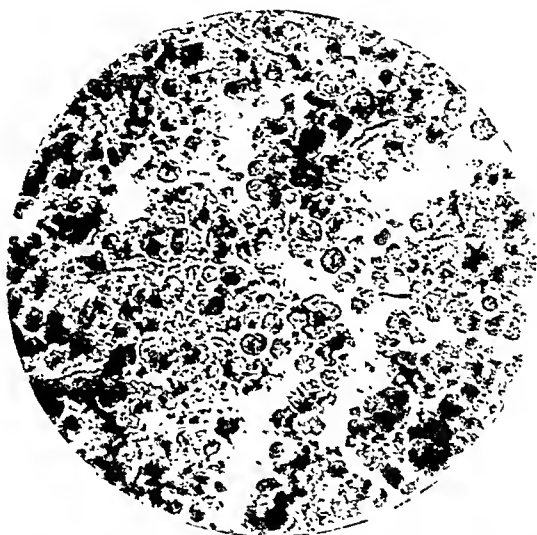


Fig. 171.—Case I. Photomicrograph of adenoma, showing uniform type of cell, small nucleus, much protoplasm, containing acidophil granules. Note absence of normal acinous arrangement of blood-vessels.

- capsule which surrounds it, and presents as a small mulberry mass about the size of a pea. At the lower surface of the tumor there is a fairly definite cyst which ruptured on removal, and extruded a semifluid gelatinoid material. The pituitary and tumor were removed *en masse* with the surrounding bone of the sella turcica. The tumor itself is about the size of a small lemon, soft, with a definite capsule, and on its upper surface the pituitary gland presents as a small flattened, ribbon-like affair that is difficult to differentiate from the tumor

mass. The optic chiasm is flattened and extends back to the corpora mammillaria which are crowded posteriorly and also flattened. The tumor is vascular.

On *histologic examination* the tumor is seen to be composed almost entirely of cells closely resembling the typical acidophil cells of the anterior lobe. The arrangement in acini is very imperfect and connective-tissue stroma very scanty. Blood-vessels are reduced in number and only moderately filled with blood-corpuscles. The generous protoplasm of the acidophil cells is packed with coarse acidophilic granules, the small compact nucleus being eccentrically placed. They vary considerably in size. Less than 1 per cent. are basophil and chromophobe cells, the latter being the more numerous. The mulberry-like mass presents a similar histologic appearance without evidences of malignancy. A small remnant of the anterior lobe is found compressed between the adenoma and the pars intermedia.

The other pathologic findings are: chronic obliterative tuberculous pericarditis, with cardiac hypertrophy and dilatation; lobular pneumonia with gangrene of the left lower lobe; chronic fibrous tuberculosis of lungs and lymph-nodes, and chronic fibrous pleurisy.

Case II. (Phila. Gen. Hosp., Autopsy No. 6286.) Very Early Acromegaly, Diagnosed Clinically by Recent Clubbing of Fingers and Separation of Lower Teeth, with Suggestive Facies. No Symptoms of Cranial Disturbance. Death from Pneumonia and Lung Abscess. At Autopsy, Hyperplastic Pituitary, Chiefly Due to Acidophil Cells of Anterior Lobe.—*History*.—E. F., white, aged forty-three, janitor, admitted to the service of Dr. Sailer and Dr. F. E. Ahlfeldt in the Philadelphia General Hospital on September 30, 1921, suffering from cough, dyspnea, and blood-spitting.

Beginning acromegaly was suspected by Dr. Sailer on account of the patient's facies and markedly clubbed fingers, and the diagnosis strengthened by the fact that the patient's lower teeth were considerably separated and that the spaces had only begun recently to increase. Unfortunately the patient's

pulmonary condition was too extreme to permit proper pituitary tests. Neither he nor his friends had noticed any changes in his appearance other than those mentioned.

The patient had been a motorman until he had a bad attack of influenza in 1917, from which he never recovered. Had only been able to do the lightest janitor's work for two years, suffering from a bad cough with copious expectoration, loss



Fig. 172.—Case II. Showing separation of teeth of lower jaw.

of weight, and evening rises of temperature. For a week before admission these symptoms had been worse, with blood-tinged sputum.

He had had scarlet fever and otitis media at sixteen. Habits irregular, but denied venereal disease. His mother died of influenza in 1917, and one brother of "galloping consumption."

Examination.—Patient prefers sitting posture and is very

dyspneic. Pupils irregular, but react promptly to light and accommodation. No disturbance of vision. Hair normal. Teeth in bad shape and lower teeth widely apart. Tongue normal. Thyroid not palpable. Fingers short and fat, with marked clubbing of tips. Toes also clubbed. The lungs show signs of consolidation of left base and impairment of left apex. The heart is enlarged, with a systolic murmur transmitted to the axilla. The electrocardiogram shows left ventricular pre-

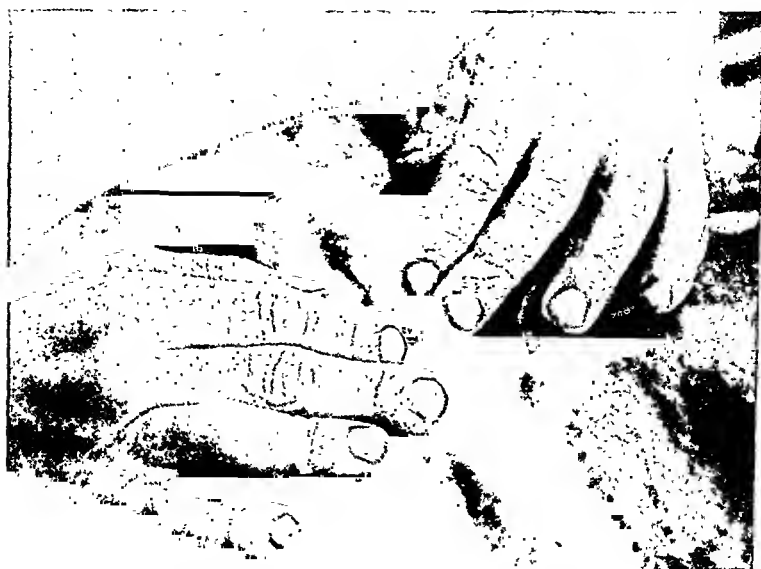


Fig. 173.—Case II. Showing clubbing of fingers.

ponderance. Leukocytes 34,400, polynuclears 82 per cent., lymphocytes 17 per cent., mononuclears 1 per cent., R. B. C. 5,120,000. Wassermann 4+ in all antigens. Blood-pressure 110/70. Urine: heavy trace of albumin, hyaline casts. In spite of digitalis and neo-arsphenamin, the patient grew steadily weaker and died from pulmonary edema.

Clinical Diagnosis.—Beginning acromegaly, lobar pneumonia, chronic mitral endocarditis, and nephritis. Syphilis, pulmonary edema.

Autopsy (Drs. Weiss and Patten).—Meninges normal except for pial thickening of interpeduncular space. Skull normal. Brain weight 1475 grams, and is apparently normal. The



Fig. 174.—Case II. Base of skull, with enlarged, deepened pituitary fossa.

pituitary body, cupped on the superior surface, is distinctly enlarged, measuring $17 \times 12 \times 7$ mm. The post lobe is of normal size, and the infundibulum is normal, but somewhat to the left

of the midline. The sella turcica is unusually deep, with a normal floor, and slight hypertrophy of the postclinoid processes.

On *histologic examination* the acidophil cells are found to be greatly predominating in almost one-half (20 out of 45 low-power fields) of a frontal section of the anterior lobe. This predominance is especially marked in symmetric postero-

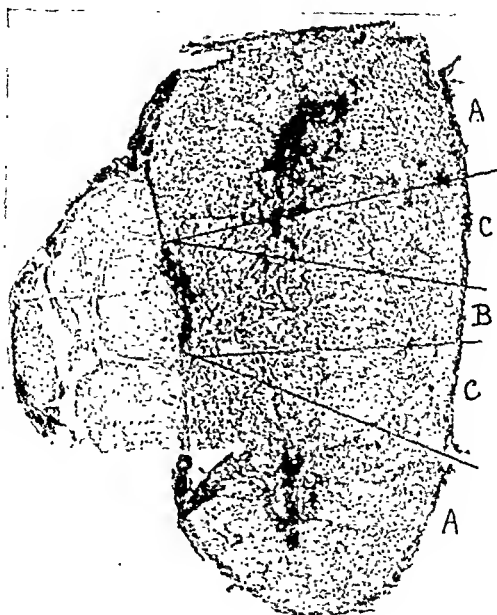


Fig. 175.—Case II. Frontal section of pituitary, showing hyperplasia due chiefly to acidophils. Areas of the three types of cells: (A) acidophils greatly predominant; (B) basophils numerous; (C) chromophobe cells (degenerated chromophils(?)) predominant.

lateral areas of the anterior lobe (Fig. 175), but is not limited by a connective-tissue framework that extends fanwise from the pars intermedia. In these areas acidophils were computed to comprise 83.7 per cent.; basophils 3.4 per cent.; chromophobe cells 12.9 per cent. In a mesial belt of the same section (occupying 7 of 45 low-power fields) basophils are much more prominent, though acidophils and chromophobes are still to be found

in considerable numbers (acidophils, 17.9 per cent.; basophils, 53.6 per cent.; chromophobe cells, 29.5 per cent.). The basophils showed a slight tendency to vacuolization. In the intermediate areas chromophobe cells are more numerous. Many of these, however, are large cells with all the characteristics of a chromophil cell except the granules, so that it seems probable that they are altered or degenerated cells of the acidophil or basophil type. A differential count in these regions reveals: acidophils,



Fig. 176.—Case II. High power of area A in Fig. 175. All the larger cells and many of the smaller are acidophils, the remainder chromophobes.

7.5 per cent.; basophils, 13 per cent.; large chromophobes(?), 30 per cent.; small chromophobes, 49.5 per cent. It is therefore obvious that not only is the anterior lobe considerably increased in size but also that the proportion of acidophils within the lobe is also considerably increased above normal. Blood sinuses are greatly increased in size and number in many areas.

The following body measurements are pertinent: Length, 170 cm.; weight, 190 pounds; circumference of head, 80 cm.; length of nose, 7 cm.; torso-leg ratio, 45.6 x 96.2 cm.; length of arm, 36 cm.; of forearm, 30 cm.; of hand, 21 cm.; of middle

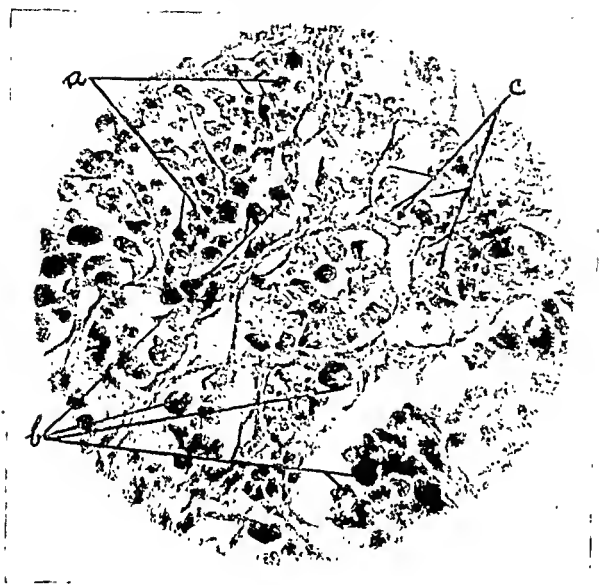


Fig. 177.—Case II. Area *B* in Fig. 175: *a*, Acidophils; *b*, basophils; *c*, chromophobes.



Fig. 178.—Case II. Area *C* in Fig. 175, lettering as in Fig. 177.

compressed layer of glandular tissue on one side. The optic chiasm was stretched over the belly of the cyst.

Histologic examination of this area showed atypical acinous epithelial cells, with large nuclei, varying considerably in size, and in a few instances undergoing mitosis. They were not enclosed in acini, but interspersed with varying amounts of connective tissue that produced not infrequently an effect of clumping. This connective tissue was both of a sparse cellular and dense fibrous type. The wall of the cyst was not lined with cells. A few other microscopic cysts were also found.

The autopsy also disclosed a marked congestion of the abdominal viscera. The thyroid, thymus, adrenals, and pancreas were normal. The testicles showed an increased amount of connective tissue between the lobules. An acute interstitial nephritis was apparently the cause of death.

Case IV. (Pa. Hosp., Autopsy No. 1126, Bull. Ayer Clin. Lab., Phila., 1908, No. 5, p. 32.) No Signs of Acromegaly or Other Disorders of Pituitary Function. Signs of Intracranial Pressure for Six Months. Death from Acute Endocarditis and Bronchopneumonia. At Autopsy a Chromophobe Adenoma of the Anterior Lobe of the Pituitary, With Preservation of the Compressed Anterior and Posterior Lobes.—*History*.—W. B., aged forty-three, negro, laborer, admitted to Pennsylvania Hospital August 11, 1908, during the service of Dr. Newlin. His family history was negative. He was born in the eighth month of pregnancy, and was weak till he was ten or twelve years old. He had temporary lateral curvature of the spine, which he outgrew. At eighteen he was strong and healthy. He always worked at hard manual labor. His wife, married ten years ago, says he was as corpulent and strong then as at present. She had one abortion in the seventh month of pregnancy, and had one child which lived only a few hours. Venereal history was denied. Sexual habits normal. The patient always drank to excess and smoked tobacco. "He always seemed to suffer in the top part of his head," and has always had headaches since a small boy. These have been worse since his skull was fractured (?) by a blow from an iron gate, three years ago.

spacing, the lower teeth do not. Hair of scalp and body normal. Ears, nose, tongue, and mouth very large. Does not appear to be mentally acute. Enlargement of upper extremity involving distal ends of radius and ulna. Hands large and spade-like, with thickening of finger pads, but have not lost their symmetry.



Fig. 179.—Case III. Cyst wall with infiltrated carcinomatous tissue.

Grip weak. Feet are tremendously enlarged (30.5 cm. long). Wassermann negative.

At Autopsy (Dr. Samuel).—The skull was found to be relatively thinner than the other bones. The sella turcica was broadened and thickened. The pituitary was replaced by a cyst under tension, measuring 4 x 6 x 3 cm. in diameter. The walls were very thin and translucent, with evidence of a thin,

only half below this constricting girdle was visible. The cut section of this tumor mass bulges, is moist, and of a reddish flesh color. The optic chiasm and tracts are much stretched and attenuated by pressure from the tumor. On separating the



Fig. 180.—Case IV. Base of brain, showing chromophobe adenoma of pituitary. (From Bulletin of the Ayer Clinical Laboratory of the Pennsylvania Hospital.)

loose connective tissue which joins them to the tumor it can be lifted out of its socket except for a long, thin, delicate pedicle joining it to the base of the brain.

On *histologic examination*, sections from all parts of this tumor show a very cellular tissue that varies but little in different

parts. Remnants of both portions of the normal gland are found stretched about it like an envelope, with columns of compressed cells in the anterior lobe. The tumor is bounded by a fairly thick, regular capsule, which in no place appears to be infiltrated by the cells of the mass of the tissue. The tumor-cells have a small round,

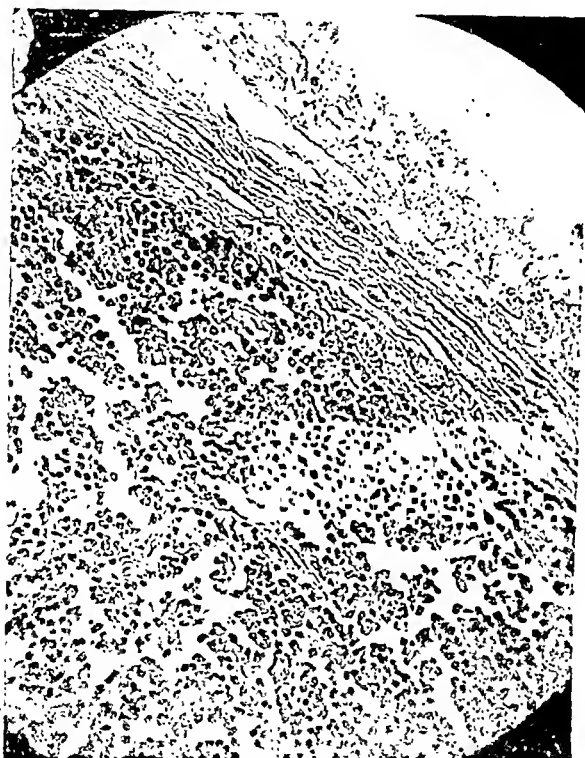


Fig. 181.—Case IV. Encapsulated adenoma, composed of small chromophobe cells.

highly chromatic nucleus and either no visible protoplasm or considerable homogeneous protoplasm, the latter appearing not unlike a plasma-cell. Nothing approaching chromophil granules is demonstrable by ordinary or special stains. Frozen sections and teased specimens show the same character of cell. The interstitial tissue is very scanty for the most part, showing as ex-

tremely fine, delicate blue fibers (Mallory's stain), or occasionally short sections of fairly small trabeculæ. Special stains for neuroglia fibers (Weigert and Mallory), myelin sheaths (Weigert), and elastic fibers (Verhoeff) fail to show their presence. Small capillaries are fairly numerous in some sections (especially those from the superior and posterior portions), but are very sparse in other parts. A very few larger vessels

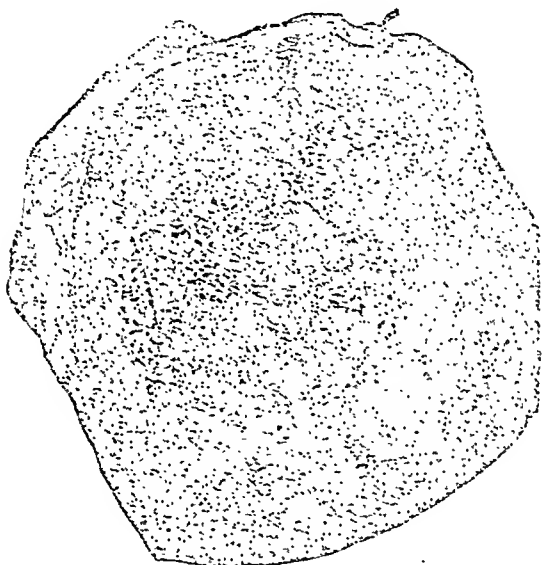


Fig. 182.—Papillary cystadenoma, arising probably from hypophyseal duct. No symptoms; discovered accidentally at autopsy.

are found in the tissue, but even in these only a few scattered elastic fibers can be found.

In addition, the autopsy showed an acute vegetative mitral endocarditis, lobular pneumonia, marked congestion of viscera, chronic mitral and aortic endocarditis with cardiac hypertrophy, chronic pleurisy, and arteriosclerosis. The other glands of internal secretion were normal, except for a marked congestion

of the parathyroids, and localized areas of fibrosis in the testicles, which were equalled by sclerotic changes in other organs.

Case V. (Phila. Gen. Hosp., Autopsy No. 6048.) Failing Vision Beginning Three Years Ago and Progressing to Total Blindness, With Coincident Signs of Hypo-post-pituitarism. No Relief from Decompression Operation. Cause of Death: Brain Tumor. At Autopsy, Cyst of Pituitary With Destruction of Both Lobes and of Optic Chiasm. Visceral Hypoplasia.—*History*.—P. J., mulatto, aged twenty-nine, stevedore, admitted to the service of Dr. Lloyd and Dr. L. E. Henderson in the Philadelphia General Hospital December 12, 1920, complaining of lost vision and headaches. His eyesight began to fail in 1918 after a severe attack of influenza. It got better in the spring of 1919, and he was able to work till April 1920, when it became so bad that he could not see enough to get around. It grew gradually worse until two weeks before admission, when spells of weakness and staggering supervened. He has been subject to frontal headache since he was "beaten up" in a riot four years ago, but headaches have been much worse since May, 1920. He states that he has not had an erection for four years and had no sexual desire for two years. He always feels cold and generally uncomfortable, and has recently had several sudden attacks of projectile vomiting.

He had measles as a child and influenza in 1918. Admits gonorrhea, but denies any other venereal disease. He stopped smoking cigars some time ago and never drank. He had eye trouble in 1916, but was greatly improved after his eyes were refracted at the Wills' Eye Hospital. His wife and 2 children are healthy; his family history negative.

Examination.—Is well nourished, but the fat distribution of feminine type, body hair sparse, and external genitalia somewhat undeveloped. The left pupil larger than right, laterally oval and reacts very slightly to light, while the right pupil fails to react. Vision in left eye 1/45, with concentric contraction of visual field. Right eye blind. No extra-ocular or other motor palsies. Sensation, including taste and smell, not impaired. Reflexes normal, except for absent Achilles' jerk. Babinski negative.

Hearing and Bárány tests normal. Sugar tolerance increased (on three occasions 150, 200, and 250 gm. of glucose failed to appear in the urine). α -Ray (13,309) shows sella turcica greatly enlarged and floor almost entirely destroyed. Urine and Wassermann negative. Hemoglobin, 70 per cent.; R. B. C., 3,810,000; leukocytes, 9200 (polynuclears 51 per cent.). Blood-pressure 96/60.



Fig. 183.—Case V. Base of skull, with enlarged sella turcica communicating with left sphenoidal sinus. Internal carotid arteries indicated by probes.

With a fairly certain diagnosis of pituitary disease, a subtemporal decompression was then performed, as the more dangerous attempt at extirpation did not seem justifiable with the advanced state of the optic atrophy. This gave only temporary relief, and the administration of pituitary extract proved entirely ineffectual. Some three months later he gradually

grew weaker, refused nourishment, and died with the usual signs of increased intracranial pressure.

At *autopsy* (Drs. Lucke and Winkelman) the body measures 165 cm. and weighs 70 kilograms. Bone development normal, but soft parts show a distinct feminine habitus (fat distribution, curved hips and thighs, mammary glands slightly prominent,

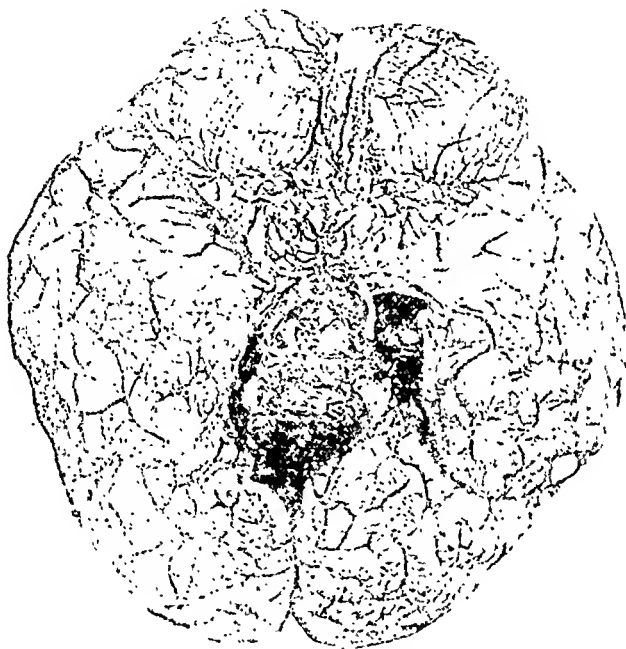


Fig. 184.—Case V. Base of brain showing large pituitary cyst, with a large lobule under right temporal lobe. The flattened chiasm constricts the center of the cyst.

etc.). Beard and mustache very scanty, with downy hair (equaling that of an average boy of fifteen). Lips fleshy. Skull, hands, and feet normal size and shape. External genitalia small.

The brain weighs 1580 grams, and is slightly edematous. At the base a large greenish mass, 5 x 9 cm., occupies the pituitary

for the past five months. During this time had developed frequency of urination and thought she passed more urine than formerly. Passed urine once every night. Had noticed no

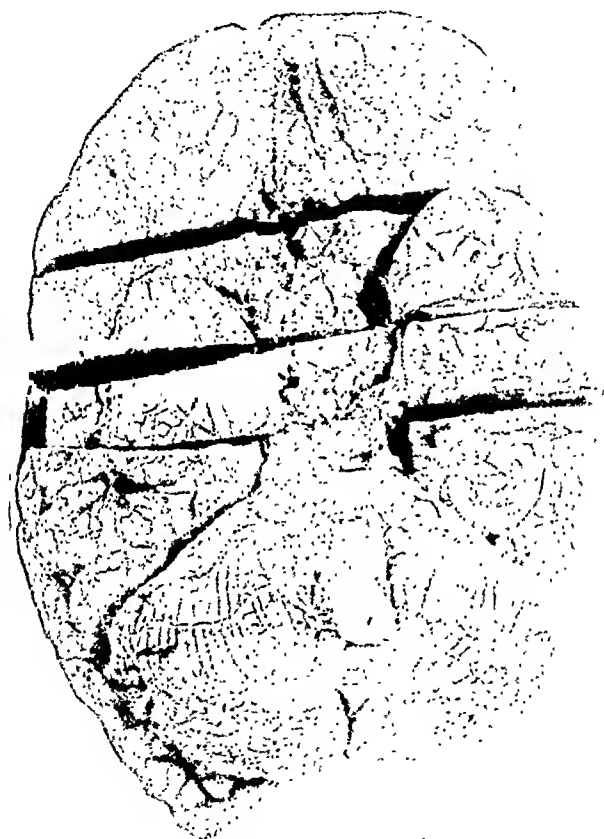


Fig. 185.—Case VI. Base of brain showing cholesteatoma in pituitary region indenting but not invading the brain tissue.

changes in size, weight, or appearance. Menstruation normal. Past history and family history negative.

On *examination* no signs of acromegaly or of hypo-post-pituitarism are found. Right pupil does not react to light or accommodation, and vision is absent. Left pupil reacts, but

vision is greatly impaired. Supra-orbital ridges tender. Nervous examination negative. Blood and urine negative. Spinal fluid Wassermann and globulin tests negative. No glycosuria after ingestion of 100 and later 200 grams of glucose. x -Ray showed great enlargement of the sella turcica, with destruction of the postclinoid processes.

Transphenoidal operation August 25th: After some difficulty in penetrating the sella, the thickened pituitary capsule was pierced, with escape of grayish-white sebaceous-like material under pressure. Condition continued satisfactory for forty-eight hours, when patient pulled out packing and blew nose vigorously. Temperature soon rose to 103° F., signs of meningitis developed, and later unconsciousness. Leukocytes 21,600. The next day the patient died, with signs of pulmonary edema.

At Autopsy (Dr. B. Lucke).—Besides a sanguinopurulent meningitis of the base of the brain (*Staphylococcus aureus*) there is found an irregular cauliflower-like, walnut-sized growth in the pituitary region. It lies superficially on the pia, denting but not growing into the brain, and extends from the pons to beyond the optic commissure and laterally to the temporal lobes. It is pearly gray, hard, brittle, and consists of many nodules the size of a small pea. The cut surface has a mother-of-pearl sheen.

On *histologic examination* the cyst wall shows rows of endothelial(?) cells, poor in nuclei and apparently undergoing necrosis. Occasionally, especially in fresh unstained specimens, are flat polyhedral cells, between which lie typical crystals of cholesterol. The fluid also gives a strongly positive cholesterol reaction. No remnants of either lobe of the pituitary can be found. The body length is 155 cm., weight 70 kilograms, frame well developed. No other points of interest are found in the other organs.

COMMENT

Case I (J. D.) is a frank case of acromegaly in which an acidophil adenoma of the anterior lobe was found at autopsy. It is therefore in accord with the theory that an increase of the acidophils, representing an increased activity of the anterior lobe, is responsible for the development of acromegaly.

Case II (E. F.), which also supports this theory, is of especial interest as an extremely early case of acromegaly, perhaps the earliest recorded that has come to autopsy. The distinct (though not extreme) hyperplasia of the anterior lobe had been sufficient to enlarge the sella turcica, but could not conceivably have exerted any increase of intracranial pressure. It is especially regrettable that time and the patient's condition did not permit a more extensive study to be made. The distribution of acidophil predominance in certain lateral areas of the anterior lobe was also of interest, as were the peculiar large cells with rarefied protoplasm in the anterior regions of the anterior lobe. It was difficult to avoid the impression that these were chromophil cells which for some unexplained reason had lost their granules. The occurrence of 83.7 per cent. acidophils in areas representing more than half of a frontal section of a grossly enlarged anterior lobe seems quite sufficient to warrant the diagnosis of acidophil hyperplasia. There is also a reasonable chance that the large chromophobe cells also had recently been actively functioning acidophils. In painstaking differential counts of the hypophysis of the woodchuck Rasmussen¹ found that the acidophils normally were slightly less numerous than the chromophobe cells, although, roughly, ten times as numerous as the basophils. I have not been able to find comparative figures for man, but certainly the proportion of acidophils is normally much less than in this case. In this connection, Lewis' case² of acromegaly with a pituitary of normal size, but with a great increase of the proportion of acidophils, should also be borne in mind.

Case III (C. V.) is a good example of how a pathologic lesion may so progress that the original etiologic factor is obscured. Assuming the correctness of the theory above given, the pituitary cyst in this case was probably preceded by an adenoma of the anterior lobe with consequent acromegaly. With carcinomatous degeneration and cyst formation, however, all such evidences were destroyed, and if the patient had lived long enough doubtless evidences of hypo-post-pituitarism would have supervened.

¹ Rasmussen, A. T., *Endocrinology*, 1921, v, 32.

² Lewis, D. D., *John Hopkins Hosp. Bull.*, 1905, xvi, 157.

It is, of course, realized that this interpretation is not capable of proof, and that the similarity of the lesions in this and in Case V might well be emphasized by opponents of this theory.

Cases IV (W. B.), V (P. J.), and VI (B. S.) are offered by way of contrast as examples of pituitary tumors that do not cause acromegaly. Case IV, a chromophobe adenoma of the

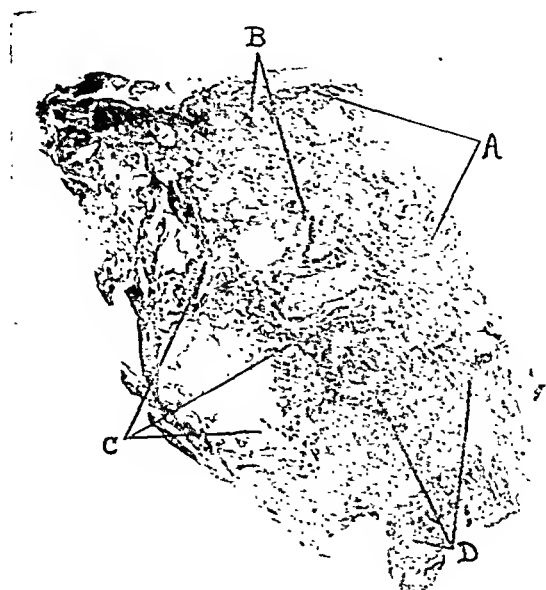


Fig. 186.—Hemorrhage into and fibrosis of both lobes of pituitary with hardly any normal tissue remaining; no symptoms were observed and the condition was discovered by accident at autopsy. *A*, Remnant of acinous tissue and anterior lobe; *B*, pars intermedia and colloid; *C*, fibrosed and fatty posterior lobes; *D*, hemorrhages in both lobes.

anterior lobe, compressing but not destroying the anterior and posterior lobes, is especially useful in bringing out this distinction, as no signs of disordered pituitary function of any kind were to be found or suspected, at least by the methods then in vogue. In Case V, a large pituitary cyst, signs of hypo-post-pituitarism and of intracranial pressure predominated from the

start. With destruction of the anterior lobe one might look also for signs of hypo-pre-pituitarism as well, but here, as in the case illustrated by Fig. 186, such signs were, as far as could be told, absent, for reasons that as yet remain unexplained. The onset of the disorder in adult life would prevent the development of skeletal infantilism, just as pure giantism is found only if hyper-pre-pituitarism occurs before normal skeletal development is finished. In Case VI, with obvious signs of increased intracranial pressure, the increased sugar tolerance and the x-ray were the only signs pointing to the pituitary, although at autopsy both lobes were found to be destroyed.

CONCLUSIONS

1. The theory that acromegaly is due to (or at least follows) hyperfunction of the anterior lobe after ossification of the epiphyses, as expressed by an increase in acidophil cells, is supported by the cases of this series as well as by the majority of those in the literature.

2. The acidophil increase may be expressed either as a hyperplasia of the normal lobe (Case II) or as an adenoma (Case I).

3. After the development of acromegaly the pituitary lesion may undergo cystic degeneration (Case III), so that lesions of this nature do not necessarily contradict the above theory. Hyperplasia or tumors of accessory hypophyses must also be taken into consideration in apparent exceptions.

4. Pituitary tumors may exist for many months even to the extent of destroying both lobes, without giving obvious signs of so-called pituitary disease. It is probable, however, that in most or all of these cases careful functional tests would reveal a latent disorder.

5. A more precise terminology than that now in use is recommended for the better discussion and elucidation of disturbances in pituitary function.

I wish to thank the several clinicians and pathologists mentioned for their courtesy in allowing this use of their material.

